The Japanese Society for Hereditary Tumors Guidance: Hereditary cancer syndrome with Multigene Panel Testing (MGPT), 2025 Edition

Edited by:
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On the Occasion of Publication

The concept of “inherited cancer” has been recognized for over a century, but it is not an exaggeration to say that awareness within the general medical community has remained limited until recently, with the exception of a few well-known hereditary cancer syndromes. Since the 1990s, with significant advancements in clinical genetics and genetic analysis technology, awareness of hereditary cancer syndromes has increased worldwide. Risk-reducing surgeries for hereditary breast and ovarian cancer has rapidly disseminated, primarily in the United States, eventually gaining insurance coverage in Japan. Furthermore, in Japan, comprehensive cancer genome profiling tests have been provided since 2019, highlighting the urgent need to establish appropriate protocols for managing secondary findings (germline findings).

The Japanese Society for Hereditary Tumors has consistently conducted basic and clinical research on hereditary tumor syndromes for over 30 years since its establishment. The society has also continued to emphasize the importance of responding to patients with hereditary tumor syndromes and their families in a multidisciplinary manner and has developed various projects related to human resource development since its inception. Effective management of hereditary cancer syndromes is supported by four key pillars: (1) accurate diagnosis, (2) appropriate treatment, (3) lifelong surveillance, and (4) responses to blood relatives. In Japan, however, the (genetic) diagnosis of hereditary tumor syndromes itself has not been disseminated sufficiently to provide adequate medical management for patients with hereditary tumor syndromes in clinical practice (regardless of their cancer status).

In other countries, information obtained through the risk assessment of hereditary cancer syndromes is used for the management of individual health. Specifically, the usefulness of multigene panel-based genetic testing, which analyzes several to dozens of genes simultaneously, has been widely recognized among the methods of risk assessment. However, there have been few guidelines or little guidance for multigene panel testing. In March 2023, the Japanese Society for Hereditary Tumors decided to create Clinical Practice Guidelines for Multigene Panel Testing (tentative name), mainly through the Academic and Education Committee. Subsequently, we began preparing the guidelines in collaboration with MHLW Research on Promotion of Cancer Control Program Grant Number JPMH　23EA1037With the efforts of all parties involved, the guidelines have been successfully finalized for publication on schedule, albeit within a short period of time. In particular, I would like to express my deepest gratitude to the individuals and related societies for conducting an external evaluation within a very limited period of time.

I hope that medical professionals and researchers involved in hereditary tumor syndromes and cancer genome medicine will find this guide to be a valuable resource that can enhance the quality of medical care for hereditary tumor syndromes. Ultimately this will contribute to the management and promotion of the health of patients with hereditary tumor syndromes (including those who have not developed cancer) and their blood relatives.

March 2025

Hideyuki Ishida, Chairman of the Board (2020-2025)
The Japanese Society of Hereditary Tumors

Preface

The present guide has been created to promote appropriate use of multigene panel testing (MGPT) in the treatment of hereditary cancer syndromes, with the aim to provide optimal, individual care for individuals with hereditary cancer syndromes in Japan.

In recent years, advances in the speed and affordability of next-generation sequencers have accelerated, and in 2013, the U.S. Supreme Court made a ruling that deemed Myriad Genetics, Inc. ineligible for patent protection on *BRCA1*/*BRCA2* genes. In light of these developments, the mainstream genetic testing for diagnosing hereditary cancer syndromes overseas has shifted to MGPT from the traditional approach, which examines multiple genes based on family history and clinical findings. The use of MGPT in Japan has steadily increased since its introduction into medical practice as a clinical testing around 2017.

To date, guidelines for hereditary cancer syndromes have been published both in Japan and overseas, covering either the syndromes as a whole or focusing on specific organs. However, to date, no guidelines have comprehensively summarized the evidence for genes associated with hereditary tumor syndromes, including those with low to moderate susceptibility.

The Academic and Education Committee of the Japanese Society for Hereditary Tumors sought an approach to comprehensively present information on genes associated with hereditary tumor syndromes, as well as their handling in clinical practice. Although some raised concerns that comprehensive guidelines for MGPT had not yet been established overseas and that it would be difficult to develop such guidelines in Japan, the Board of Directors of the Japanese Society for Hereditary Tumors decided to create the guideline on hereditary cancer syndromes and MGPT. In 2024, we began preparing the present guidance for publication in collaboration with the Japanese Society for Hereditary Tumors as MHLW Research on Promotion of Cancer Control Program Grant Number JPMH　23EA1037.

This guidance was prepared through lively debate among the committee members, reaching a consensus by respecting the diverse expertise of each member and holding earnest discussions. I would like to express my deepest gratitude to everyone involved for their outstanding efforts in developing the world's first clinical guideline for hereditary cancer syndromes.

In Japan, cancer genome medicine is defined as "medical care that optimizes treatment, predicts prognosis, and prevents disease onset by using genome information obtained from tumor and normal sites of cancer patients (cancer genome medicine may also be provided to individuals who have not developed cancer, and it includes multi-omics information outside genome information.)" [From the 'Report of the Consortium Meeting for the Promotion of Cancer Genome Medicine: Towards the Construction of Cancer Genome Medicine with the Participation of the Public' (source: Ministry of Health, Labour and Welfare website, June 27, 2017)]. In Japan, cancer gene panel tests have been covered by insurance since June 2019, marking the beginning of the full-scale operation of cancer genome medicine aimed at optimizing treatment. However, it could be contended that the true inception of cancer genome medicine in Japan will occur when the utilization of genetic information for disease prevention is widely introduced into actual clinical practice, even for individuals who have not developed cancer.

This guidance does not divide patients with hereditary cancer syndromes into cancer-free and cancer-affected individuals. Rather, it has been created based on fundamental concepts that hereditary tumor syndromes are genetic traits that predispose to cancer onset, that cancers associated with genetic variants are one of the phenotypes, and that hereditary tumor syndromes can only be diagnosed by genetic testing.

Although genetic information belongs to each individual, it is also shared among blood relatives. For this reason, I believe that treating hereditary tumor syndromes represents the essence of family and community medicine. Thus, using this guidance as a foundation, various efforts are needed in the future, including strengthening the medical treatment system for hereditary tumor syndromes, training medical professionals, and sharing information with the public. Also, I hope to realize a society where appropriate medical care is provided to anyone who wishes to know their risk of developing tumors.

I hope that this will serve as a useful guide for all medical professionals involved in the treatment of hereditary cancer syndromes in their daily practice. Thus, this guidance should serve as a foundation for future efforts, including strengthening the medical care system for hereditary cancer syndromes, training healthcare professionals, and promoting public awareness.

March 2025

Akira Hirasawa, Principal Investigator

MHLW Research on Promotion of Cancer Control Program Grant Number JPMH　23EA1037

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- Japanese Society for Gene Diagnosis and Therapy
- Japanese Cancer Association
- Japanese Society of Cancer Nursing
- Japan Society of Clinical Oncology
- Japan Society of Human Genetics
- Japanese Association of Certified Genetic Counselors
- Japanese Society of Laboratory Medicine
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In preparing this guidance

1. Purpose of this guidance

The present guidance is intended to assist healthcare providers performing multigene panel testing (MGPT) for hereditary cancer syndromes and to support individuals undergoing MGPT, along with their blood relatives, in making informed, shared decisions about MGPT and subsequent care. In addition, the guidance discusses responses to individuals diagnosed with (and those suspected of having) hereditary cancer syndromes based on gene-related tests for the purpose of selecting cancer drug therapy. It also explores the national project "Action Plan for Whole Genome Analysis 2022," as well as issues related to the diagnosis of hereditary tumor syndromes.

With the advancements in gene sequence analysis technology and reducing costs, MGPT, which can analyze multiple cancer susceptibility genes simultaneously, has gained greater popularity in Western countries than syndrome-specific genetic testing (SSGT), which targets cancer susceptibility genes that cause specific hereditary cancer syndromes. MGPT is a clinical test that simultaneously analyzes multiple germline genes with cancer susceptibility, and it can be broadly classified into two types: cancer-specific panel and comprehensive cancer panel (**Figure 1-2 in Overview 1**). Japan has also seen a gradual increase in the opportunity to use MGPT for diagnosing hereditary cancer syndromes in clinical practice. However, one of the challenges in MGPT-based treatment has been the fact that the testing covers genes for which there are currently no standards for risk management.

Thus, there is an increasing need for cross-organ and cross-department management guidelines for treating hereditary cancer syndromes and cancer susceptibility genes included in MGPT, which led to the creation of the present guidance. Due to the characteristic of hereditary diseases, hereditary cancer syndromes diagnosis involves responses to individuals and their blood relatives, including even those who have not developed cancer. In addition, some items discussed in this guide currently lack medical evidence and consensus in medical implementation in Japan; therefore, those items are intended to be used as an indicator or reference for clinical responses.

2. Contents of this guidance

Hereditary cancer syndromes represent diseases and pathological conditions caused by abnormalities in cancer susceptibility genes, which carry a genetic predisposition to develop cancer. Individuals with hereditary cancer syndromes often present with neoplastic lesions and phenotypes in multiple organs. Numerous cancer susceptibility genes associated with hereditary cancer syndromes have been identified, each characterized by varying degrees of organ specificity and penetrance. The present guidance provides an overview of each hereditary cancer syndrome based on the evidence reported to date and outlines cancer caused by each hereditary cancer syndrome. This guidance consists of the following five chapters:

Chapter 1: "Introduction to hereditary cancer syndromes"
Chapter 2: "Genetic testing and clinical practice systems for the definitive diagnosis of hereditary cancer syndromes"
Chapter 3: "Organ-specific management of hereditary cancer syndromes"
Chapter 4: "Causative genes of hereditary cancer syndromes and their management"
Chapter 5: "Materials"

Additionally, topics anticipated to become future issues, though not yet implemented in Japan, are briefly summarized in the Column section. Commentary has also been provided in the side notes to highlight challenges encountered in clinical practice and to promote a clearer understanding of the features and

terminology associated with MGPT.

3. Process of preparing this guidance

The Japanese Society for Hereditary Tumors began working on the development of this guidance, mainly through the Academic and Education Committee. The chairpersons, oversight committee members, area leaders (in charge of each chapter), and editorial committee members were appointed for the preparation of this guidance, and a general meeting was held in May 2023. After the general meeting, the members to be involved in the preparation of the guidance (including those in charge of writing) were appointed in consideration of their expertise (**Members Involved in the Development of "Guidance for Hereditary cancer Syndrome Multigene Panel Testing (MGPT), 2025 Edition"**), and a kick-off meeting for each chapter was held in the same month. At the kick-off meeting, the overall structure of the guidance was finalized, and additional members were appointed according to the content of the guidance. In June 2023, a plenary meeting was held, starting the preparation of this guidance. Also, in November 2023, the group for MHLW Research on Promotion of Cancer Control Program Grant Number JPMH 23EA1037 In collaboration with related academic societies, organizations, and authorities, the group has worked on the development of this guidance.

4. Process of setting BQs and FQ in Chapter 2

The most important issues in MGPT-based treatment and management of hereditary cancer syndromes have been selected as background questions (BQs) by the committee members of Chapter 2. BQs cover issues related to the following systems:

- Systems for genetic testing, including MGPT for hereditary cancer syndromes
- Systems for supporting clients' decision-making through genetic counseling
- Systems for managing the risk of hereditary cancer syndromes based on genetic testing
- Systems for managing genetic information

Each BQ was set as described in the clinical algorithm associated with MGPT (**Figure 2-1 in Chapter 2**).

Additionally, a Future Research Question (FQ) was set in anticipation of impending issues that may arise in comprehensive genetic analysis.

5. Collection of evidence for risk management in Chapter 3

Focusing on genes associated with cancer and tumor susceptibility in various organs, we presented an overview on the medical management of germline pathogenic variants (GPVs) to be provided upon their detection (including methods of risk reduction and surveillance), assuming its implementation by clinicians.

The genes listed for each organ include those causing the representative hereditary cancer syndromes listed in **Table 1-1** in **Chapter 1**, as well as those selected in Chapter 4. In addition, genes that are considered important for the medical management of each organ despite not being selected in Chapter 4 are discussed in Chapter 3.

We have collected evidence from domestic and international guidelines and various literature sources, based on which we discussed medical management.

6. Collection of evidence for risk management in Chapter 4

We began working on the development of this guidance with the aim of examining the evidence for cancer susceptibility genes that are thought to be associated with hereditary cancer syndromes. We selected genes for which evidence was examined, regardless of the degree of evidence or recommendations, with reference

to the following (as of the end of July 2024):

・Genes for which genetic testing can be performed for the purpose of diagnosing hereditary cancer syndromes under insurance coverage

・Causative genes of hereditary cancer syndromes for which clinical practice policy has been established in the following domestic clinical practice guidelines or guidebooks (**Chapter 5-6, below**):

- Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition (2024)
- Guidelines for Diagnosis and Treatment of Hereditary Breast and Ovarian Cancer 2024 (2024)
- Clinical Practice Guidelines for Pheochromocytoma and Paraganglioma, 2018 Edition (2018)
- Guidebook for Management of Multiple Endocrine Neoplasia (2013)
- Clinical Practice Guidelines for Li-Fraumeni Syndrome, 2019 Edition, v1.1 (2019)
- Clinical Practice Guidelines for Neurofibromatosis Type 1 (von Recklinghausen disease), 2018 Edition (2018)
- Diagnostic Criteria and Treatment Guidelines for Tuberous Sclerosis Complex, Revised Edition (2018)
- Guide to Treatment of von Hippel-Lindau Disease, 2024 Edition (2024)
- Clinical Practice Guidelines for Cowden Syndrome/PTEN Hamartoma Tumor Syndrome in Children and Adults, 2020 Edition (2020)
- Clinical Practice Guidelines for Peutz-Jeghers Syndrome in Children and Adults, 2020 Edition (2020)
- Clinical Practice Guidelines for Juvenile Polyposis Syndrome in Children and Adults, 2020 Edition (2020)
- Clinical Practice Guidelines for Plexiform Neurofibroma/Malignant Peripheral Nerve Sheath Tumor (2024)

・Twenty-eight genes associated with hereditary cancer syndromes, among the 81 genes that are recommended to be reported to clinicians upon detection of GPVs in clinical whole-exome/whole-genome analysis, as specified in the ACMG SF v3.2 list [ACMG SF v3.2 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023 Aug;25 (8):100866 [Epub 2023 Jun 22.]]

・Genes for which germline confirmatory analysis is recommended upon detection of pathogenic variants in comprehensive tumor tissue gene analysis according to the ESMO Precision Medicine Working Group [Germline-focused analysis of tumour-only sequencing: recommendations from the ESMO Precision Medicine Working Group. Ann Oncol. 2019 Aug 1;30(8):1221-31]

・Genes listed in the following international clinical practice guidelines (the version numbers listed are the latest as of the last confirmation [July 2024])

- NCCN guidelines® Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (Version 3. 2024)
- NCCN guidelines® Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (Version 1. 2024)
- NCCN guidelines® Prostate Cancer (Version 4. 2024)
- NCCN guidelines® Melanoma: Cutaneous (Version 2. 2024)

・The *DICER1* gene (causative gene of DICER1 syndrome) was selected, as it was suggested to be associated with hereditary tumor syndromes by the attendees of the plenary meeting, which included all members involved in the development of this guidance.

The *NBN* gene was not selected for this guidance, as it was judged to have insufficient evidence of association with hereditary cancer syndromes by the attendees of the plenary meeting, which included all

members involved in the development of this guidance.

For each of the 56 genes selected for this guidance, we summarized background information, as well as medical management information on preventive interventions recommended or considered in domestic and international guidelines upon detection of GPVs that cause hereditary cancer syndromes.

7. Target population of this guidance

This guidance is primarily intended for individuals suspected of having hereditary cancer syndromes (excluding those with hereditary hematopoietic diseases) and undergoing a genetic medical assessment, individuals for whom the use of MGPT is considered, and individuals for whom MGPT and other genetic testings have confirmed the presence of GPVs causing hereditary cancer syndromes. It is intended for both cancer-unafffected and cancer-affected individuals.

8. Intended users of this guidance

This guidance is intended to be used by all medical staff involved in the treatment of hereditary cancer syndromes, including those performing MGPT, at medical institutions in Japan. Although the guide was created with an intention to be used by medical professionals, it can also be used by clients receiving genetic counseling and the general public.

9. External evaluation

In order to solicit the opinions of medical professionals, related parties, and those involved in the treatment of hereditary cancer syndromes, this guidance was externally evaluated by related academic societies and organizations, as well as the external evaluation committee, which had no conflict of interest with those involved in the writing or development of the guidance (**See p. 11**). The evaluation was made using an open-ended response format. In addition, public comments were solicited on the website of the Japanese Society for Hereditary Tumors. The points raised in the external evaluation were reviewed by the group members involved in the development of the guidance and reflected in the main text with appropriate revisions and additions. The response to the external evaluation is posted separately on the website of the Japanese Society for Hereditary Tumors.

10. Future plans (creation and revision of English version)

After the publication of the Japanese version of this guide, we plan to publish its English version internationally, aiming to make the guide more widely available in clinical practice for hereditary cancer syndromes. Genetic care and genomic medicine have been progressing at a remarkable pace, with new findings accumulated every day. As evidence is updated, we expect that it will be necessary to create a revised guidance, as well as clinical practice guidelines covering a wider range of hereditary cancer syndromes.

11. Source of funding

This guide was developed with the funding support of the Japanese Society for Hereditary Tumors, as well as MHLW Research on Promotion of Cancer Control Program Grant Number JPMH 23EA1037. No support was received from any other organizations or companies.

12. Conflict of interest

The financial and academic conflicts of interest (COI) of the members involved in the development of

"Guidance for Hereditary Cancer Syndrome with Multigene Panel Testing (MGPT), 2025 Edition" have been investigated (their financial conflicts of interest were summarized in accordance with the guidelines of the Japanese Society for Hereditary Tumors). As a result of investigating the COI status of the members through self-declaration, COI with the following companies was declared:

ACTmed Co. Ltd., Astellas Pharma Inc., AbbVie Inc., Eisai Co. Ltd., MSD Inc., Ono Pharmaceutical Co. Ltd., Kyowa Kirin Co. Ltd., Konica Minolta Inc., CMIC Co. Ltd., Daiichi Sankyo Co. Ltd., Takeda Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., Tsumura & Co., Eli Lilly Japan K.K., NEC Co., Nippon Boehringer Ingelheim Co. Ltd., Pfizer Japan Inc., Myriad Genetics, Inc.

Glossary

The 2015 ACMG/AMP guidelines

The 2015 ACMG/AMP guidelines, developed by the American College of Medical Genetics and Genomics (ACMG) in collaboration with the Association for Molecular Pathology (AMP) and the College of American Pathologists (CAP), include definitions of terms and detailed guidelines for variant classification, and they were published as follows:

Richards S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-24.

DNA mismatch repair (MMR)

Among the mechanisms for repairing DNA replication errors, DNA MMR specifically repairs non-complementary base pairs (DNA mismatches), involving at least six genes: *MLH1*, *MSH2*, *MSH6*, *PMS2*, *MLH3*, and *MSH3*. In addition, DNA replication errors often occur in the repeating sequences of one to several bases in DNA, called microsatellites. Deficient mismatch repair (dMMR) causes abnormalities in the number of microsatellite repeats, resulting in microsatellite instability (MSI). The state in which the mismatch repair function is maintained may be referred to as proficient mismatch repair (pMMR).

Germline pathogenic variant (GPV)

A GPV refers to a pathogenic variant found in the germline. The presence of a GPV in a cancer susceptibility gene indicates that the individual has a "hereditary tumor syndrome," a condition or predisposition that increases the risk of cancer onset in specific organs associated with the gene. In comprehensive genomic profiling (CGP), GPVs are detected by tumor-normal paired testing using normal sites as a control.

(See Presumed germline pathogenic variant (PGPV))

The Human Genome Variation Society (HGVS) nomenclature

The HGVS nomenclature is an internationally recognized standard format for describing sequence variants of DNA, RNA, and proteins. It is used to communicate variant information in clinical reports and to share variant information in publications and databases. The HGVS nomenclature is managed by the HGVS Variant Nomenclature Committee (HVNC) under the auspices of the Human Genome Organization (HUGO).

Laboratory developed test (LDT)

According to the U.S. Food and Drug Administration (FDA), LDT is defined as "In Vitro Diagnostics (IVD) that is certified under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 for clinical use, and it is designed, manufactured, and used in a single laboratory that meets the regulatory requirements for performing highly complex testing under CLIA. In Japan, the Japanese Promotion Council for Laboratory Testing has issued a proposal to provisionally define LDT as "a test that is designed, developed, manufactured (or modified), and used to perform testing on specimens within a single laboratory or laboratory network where test results are intended to be used to support clinical diagnosis or to make decisions regarding clinical management" based on ISO/DIS 5649. At present, a standardized definition has not been established, and discussions regarding its implementation in Japan are ongoing.

Multi-locus inherited neoplasia allele syndrome (MINAS)

Individuals with MINAS refer to those who have GPVs in two or more cancer susceptibility genes. MINAS is diagnosed more frequently by MGPT than by SSGT.

Presumed germline pathogenic variant (PGPV)

A PGPV refers to a pathogenic variant suspected to be of germline origin in CGP and some companion diagnostics that analyze tumor tissue only or free DNA in the blood.

(See Germline pathogenic variant (GPV))

Single nucleotide variant (SNV)

An SNV, formerly known as a single nucleotide polymorphism (SNP), is a single base in genomic DNA that has been changed to another base.

Variant of uncertain significance (VUS)

A VUS refers to a variant whose relationship to pathogenicity is undetermined due to insufficient accumulation of information to evaluate the pathogenicity of the variant or sufficient evidence suggestive of conflicting pathogenicity. The interpretation of results may be changed in the future.

X-linked recessive (XR) inheritance disease

An XR inheritance disease refers to a single-gene disease caused by GPV in a gene on the X chromosome. If there is one copy of GPV on the X chromosome, males develop the disease as they have only one X chromosome, whereas females develop mild or no disease as they have two X chromosomes.

Accession number

An accession number is a unique number used to identify data of base and amino acid sequences. For example, GenBank of the National Center for Biotechnology Information (NCBI) uses the NM_xxx notation to indicate specific reference sequence information of messenger RNA (mRNA). When a gene has multiple transcriptome (mRNA) sequences, the positional information on the cDNA or protein may vary, even for the same variant.

Allele

An allele refers to a paternally or maternally inherited gene or variant present at the same locus. Usually, one allele is inherited from each parent at each locus. The combination of alleles constitutes the genotype.

Allele frequency

Allele frequency indicates the occurrence frequency of a specific allele in a given population or tumor cells.

Genetic counseling

Genetic counseling is a process of assisting individuals in understanding and adapting to the medical, psychological, and familial implications of genetic involvement in disease.

Genetic testing

Genetic testing refers to tests that examine pathogenic variants or chromosomal abnormalities of genes in the human germline, as well as related tests. In other words, it refers to tests that reveal the genetic information possessed innately by an individual in the nuclear and mitochondrial genomes (information

revealed by germline genetic analysis), which in principle remains unchanged throughout life, for the purpose of making a diagnosis of single-gene diseases, risk assessment of multifactorial diseases, estimation of the efficacy, side effects, and metabolism of drugs, and genetic examination related to the identification of an individual.

■ Genotype

Genotype refers to genetic information presented as genetic characteristics of an individual. It is expressed as a DNA base sequence and is generally determined by the combination of base sequences (alleles) at one or more loci inherited from both parents. An individual carrying two same alleles is considered "homozygous," whereas an individual carrying two different alleles is considered "heterozygous."

(**See Phenotype**)

■ Hereditary cancer syndrome

A hereditary cancer syndrome is caused by carrying a GPV in a cancer susceptibility gene, and the concept of the syndrome applies to individuals who have and have not developed cancer.

■ Cancer susceptibility gene (or cancer predisposition gene)

A cancer susceptibility gene (or cancer predisposition gene) refers to a gene that increases the risk of developing cancer in the presence of GPV.

■ Cancer genome medicine

Cancer genome medicine optimizes treatment, predicts prognosis, and prevents disease onset by using genomic information obtained from tumor and normal sites of cancer patients. Cancer genome medicine may be provided to individuals who have not developed cancer, and it also includes multi-omics information outside genome information [From the "Report of the Consortium Meeting for the Promotion of Cancer Genome Medicine: Towards the Construction of Cancer Genome Medicine with the Participation of the Public" (source: website of the Ministry of Health, Labour and Welfare, June 27, 2017)].

■ Cancer-specific MGPT

In cancer-specific MGPT, target genes are selected in consideration of the risk of cancer onset in each organ.

■ Pseudogene

A pseudogene refers to a fragment of DNA that has lost its ability to encode a functional protein during evolution due to the substitution, insertion, or deletion of bases. Pseudogenes are derived from copies of normal genes, with more than 13,000 pseudogenes have been identified in the entire genome. Some are transcribed into mRNA, and a few are translated into proteins. Because their sequences are highly similar to those of original genes, it can be difficult to distinguish them during analyses, which often affects the accuracy of variant detection. Typical pseudogenes associated with hereditary tumor syndromes include *PMS2CL* (*PMS2* pseudogene) and *SDHAP1* (*SDHA* pseudogene). In actual analyses, pseudogenes are often distinguished by special analysis methods using changes in the base sequence specific to the pseudogene as a clue.

■ Client

Clients, also referred to as consultants, are individuals who receive genetic counseling, as well as their family members. They are referred to as clients rather than patients, as they may not have developed disease.

Clonal hematopoiesis of indeterminate potential (CHIP)

CHIP refers to a condition in which a group of cells originating from a single hematopoietic stem cell with a specific de novo mutation proliferate in the bone marrow and constitute part or all of the blood cells. CHIP can occur spontaneously, especially in older adults, and is often asymptomatic. It has been shown that some individuals with CHIP are at increased risk of progression to leukemia and other hematopoietic abnormalities and that CHIP is the basis for a number of diseases, including solid cancers and lifestyle-related diseases.

Act on the Promotion of Genomic Medicine

The Act on the Promotion of Genomic Medicine establishes basic policies for the promotion of genomic medicine and aims for the safe implementation and dissemination of genomic medicine. The Act, officially named the "Act on the Comprehensive and Planned Promotion of Measures to Ensure that the Public Can Receive High-quality and Appropriate Genomic Medicine With Peace of Mind," was promulgated and came into effect on June 16, 2023. The Act has greatly contributed to the maintenance of the health of the public by enabling genomic medicine to provide optimal medical care according to the individual's physical characteristics and disease conditions. Furthermore, for its dissemination, it is necessary to address issues related to protecting individual rights and interests, as well as to maintaining human dignity. In view of this, the Act aims to establish basic principles and clarify the responsibilities of the government and other parties regarding measures to ensure that the public can receive high-quality and appropriate genomic medicine with peace of mind (referred to as "measures for genomic medicine"). It also aims to promote the measures for genomic medicine in a comprehensive and planned manner by formulating a basic plan and determining other fundamental matters for the measures for genomic medicine.

Genome-wide association study (GWAS)

GWAS is a research approach that comprehensively analyzes hundreds of thousands to millions of SNVs distributed throughout the genome in order to identify SNVs that are statistically associated with a disease or a specific trait.

Structural variation (SV)

An SV refers to a structural change generally observed in regions larger than approximately 1 kb. It is a general term for genetic alterations, including copy number variations (CNVs), inversions, balanced translocations, and genomic imbalances (insertions and deletions).

Companion diagnostics

Companion diagnostics is a diagnostic technique used to predict whether a drug is effective in an individual before its administration. It utilizes methods to make a diagnosis by testing the expression levels of target molecules or biomarkers of related genes, such as SNVs and SVs. Companion diagnostics is a core concept of precision medicine and is essential for selecting the most appropriate treatment for a patient.

Surveillance

Surveillance is a detailed and systematic test for the early detection of cancer in the organs where the risk of cancer onset is estimated to be high among individuals carrying GPVs in cancer susceptibility genes. Its concept differs from that of so-called "countermeasure-type cancer screening."

Reference sequence

A reference sequence is a base sequence that serves as a standard for sequence analysis. Reference sequences are derived from the genome sequence decoded in the Human Genome Project in 2003. They are continuously updated by the Genome Reference Consortium (GRC), and recent references include GRCh38/hg38 and GRCh37/hg19. The position in the genomic DNA differs depending on the reference sequence used, even with the same coding DNA.

■ Next-generation sequencer (NGS)

An NGS is analysis equipment utilizing next-generation sequencing technology, which can simultaneously decode DNA sequences at high speed and in large quantities. Compared to conventional analysis technologies, NGSs enable detailed analysis of gene variants, expression patterns, gene recombination, and other phenomena, while significantly reducing costs and time. NGSs are used in a wide range of fields, including cancer research, diagnosis of hereditary diseases, and personalized medicine.

■ Autosomal dominant (AD) disease

An AD disease refers to a single-gene disease that occurs when GPV is present in one allele of a gene on an autosomal chromosome. One of the parents of patients with an AD disease often carries a GPV. An AD disease is passed on from a GPV-carrying parent to the child with a probability of 50%.

■ Autosomal recessive (AR) disease

An AR disease refers to a single-gene disease that occurs when GPV is present in both alleles of a gene on an autosomal chromosome. Basically, both parents are GPV carriers with no disease onset. The disease develops in individuals who inherit one GPV from each parent. There is a 25% probability that a child from GPV-carrying parents carries GPV at both alleles and develops the disease.

■ Single-site testing

Single-site testing is a genetic test that analyzes the presence or absence of certain variants in a gene. It is used to determine whether a variant identified in a proband with a genetic disease is shared by blood relatives and to examine whether a PGPV detected by CGP is a GPV.

■ Penetration rate

Penetration rate refers to the probability of expressing the phenotype that corresponds to the genotype in a population with the same genotype for a single-gene disease. Complete penetrance refers to a situation in which the probability of expressing the phenotype is 100%.

■ Germline findings

Germline findings refer to germline-related information detected by different tests and analyses, regardless of their intended purpose. They correspond to GPVs and PGPVs detected by CGP, and germline findings in this guide include both.

(See Secondary findings)

■ Germline variant

A germline variant refers to a change in DNA sequence inherited through sperm or eggs. Germ cells refer to sperm and eggs. Sperm and eggs, also called gametes, are cells that transmit genetic information to the next generation. Because germline variants are present at the fertilized egg stage, the same change occurs in all cells throughout the body.

(See Somatic variant)

Homologous recombination repair (HRR)

HRR is a mechanism of DNA damage repair that repairs DNA double-strand breaks. It repairs damaged sites by using DNA with homologous sequences of opposing alleles as a template. Genes involved in HRR are collectively referred to as HRR genes.

(See Homologous recombination deficiency (HRD))

Homologous recombination deficiency (HRD)

HRD is a condition in which the function of HRR genes is abnormal. HRD is often evaluated by calculating the tumor genomic instability score and performing variant analysis of *BRCA1* and *BRCA2* (including large-scale reconstruction).

(See Homologous recombination repair (HRR))

Somatic variant

A somatic variant refers to an acquired change in the base sequence that occurs in non-germ cells that make up the body (somatic cells). The genetic information of somatic cells is not passed on to the next generation.

(See Germline variant)

Multigene panel testing (MGPT)

MGPT is a genetic test that simultaneously analyzes a large number of genes. It is used to evaluate the risk of developing diseases, such as cancer, cardiovascular diseases, and rare diseases, in addition to predicting prognosis and optimizing treatment. The present guide focuses on MGPT for hereditary tumor syndromes.

Syndrome-specific genetic testing (SSGT)

SSGT is a test that examines only the genes selected based on the phenotype. SSGT often targets one to several genes.

Secondary findings

"Recommendations on the Information Transmission Process in Genomic Medicine – Part 1: Focusing on Cancer Gene Panel Testing (Revised 2nd Edition)" defined a secondary finding as "the finding of a germline variant (gene mutation*) that can be determined to be pathogenic by so-called 'cancer gene panel testing' performed to detect somatic variants (somatic mutations*) in cancer cells for the purpose of diagnosis, treatment, and prognosis prediction of cancer" (* indicates original wording). In recent years, the term "germline findings" tends to be more commonly used internationally than "secondary findings."

(See Germline findings)

"Guidelines for Genetic Testing and Diagnoses in Medical Care" released by the Japanese Association of Medical Sciences

"Guidelines for Genetic Testing and Diagnoses in Medical Care" (revised in March 2022) summarize basic items and principles that medical professionals should keep in mind in order to appropriately and effectively conduct genetic testing and make diagnosis, with due attention and consideration given to the characteristics of genetic information.

Variant

Variants represent individual differences in DNA sequences. Variants include those that are considered causative of disease, those that are not considered causative of disease, and those whose causative nature cannot be currently determined. Pathogenic variants (mutations) in genes include those in the germline and those acquired in somatic cells.

(See Mutation, Germline variant, and Somatic variant)

Phenotype

Phenotype refers to a trait or characteristic of an individual that is actually observed under the influence of the genotype. Individuals with the same genotype do not necessarily exhibit the same phenotype.

(See Genotype)

Pathogenicity interpretation

Pathogenicity interpretation is a process of evaluating the pathogenicity of a variant. The ACMG recommends that the 2015 ACMG/AMP guidelines be used as a reference for the evaluation of pathogenicity. In recent years, new methods for evaluating pathogenicity in individual genes or variant characteristics have also been proposed separately by the U.S. Clinical Genome Resource (ClinGen) and other programs.

Analytic validity

Analytic validity serves as an indicator of the accuracy and reliability of a test. It consists of four elements: analytic sensitivity, analytic specificity, laboratory quality control, and robustness.

Heterozygote

Heterozygote refers to an individual who carries GPV in only one allele for the causative gene of a given genetic disease. Heterozygous individuals with autosomal dominant inheritance are those who have developed the disease or GPV carriers who have not developed the disease, whereas heterozygous individuals with autosomal recessive inheritance are GPV carriers.

(See Homozygote)

Mutation

In the medical field, a mutation is considered to be a pathogenic variant. However, the term has fallen out of use in recent years.

(See Variant)

Comprehensive MGPT

Comprehensive MGPT broadly targets genes associated with hereditary tumors.

Comprehensive genomic profiling (CGP)

CGP is a test that comprehensively profiles the genome through the analysis of variants in a large number of genes using next-generation sequencers and other tools. In cancer treatment, CGP can be broadly divided into two categories depending on the clinical position: (multiplex) companion diagnostics and (comprehensive) genomic profiling testing. In this guide, CGP is defined as a test that analyzes variants in more than 100 cancer-related genes in tumor tissues and cells of solid tumors or peripheral blood, aiming to obtain information on therapeutic drugs and clinical trials for the genetic changes. In addition, cancer gene panel testing may be used nearly interchangeably with CGP.

Homozygote

Homozygote refers to an individual who carries GPV in both alleles for the causative gene of a given genetic disease. It is the state of having the same alleles at the same locus. Homozygous individuals with autosomal recessive inheritance have a high risk of disease onset. Homozygous individuals with autosomal dominant inheritance tend to suffer from embryonic lethality or to develop the disease with greater severity or at a younger age than heterozygous individuals.

(**See Heterozygote**)

Polygenic risk score (PRS)

PRS is used to evaluate polygenic diseases and predispositions by considering variants in a large number of genes. Polygenicity indicates the involvement of variants in a large number of genes, whereas monogenicity indicates the involvement of variants in a single gene.

Comprehensive genome analysis

Comprehensive genome analysis is a sequence analysis method that targets a wide range of regions, such as the entire gene or genome region. The term is used in contrast to sequence analysis that targets limited regions (tens to hundreds of genes), such as multigene panel testing (MGPT) and cancer genome profiling testing.

Mosaicism

Mosaicism is a state in which cells with and without variants coexist due to de novo mutations during cell division, although they are derived from a single embryonic cell. Mosaicism is divided into two types: “somatic mosaicism,” in which genetic changes occur in somatic cells during embryonic development, and “gonadal mosaicism,” in which variants are present only in some of the gonads (testes and ovaries). In somatic mosaicism occurring early in embryonic development, variants may also be present in the gonads. Parents with pathogenic variants in gonadal cells can potentially pass GPV to their offspring.

Clinical validity

In genetic testing, clinical validity serves as an indicator of the significance of test results. “Guidelines for Genetic Testing and Diagnoses in Medical Care” (revised March 2022) state that clinical validity is “evaluated based on information such as sensitivity (positive rate in the presence of disease), specificity (negative rate in the absence of disease), disease prevalence, positive predictive value, negative predictive value, and relationship between genotype and phenotype.

Clinical utility

Clinical utility serves as an indicator that should be considered when assessing the merits and demerits of introducing gene-related testing into daily clinical practice. It includes all elements, such as the natural history of the target disease, availability of effective treatment, assurance of accuracy, pilot studies, health risks, economic evaluation, facilities, education, monitoring, and evaluation.

(in Alphabetical and Japanese syllabary order)

Abbreviations

＊：Frequently used abbreviations in this guidance

*	ACCE	Acronyms of “analytic validity,” “clinical validity,” “clinical utility,” and “ELSI”
	ACGS	Association for Clinical Genomic Science
*	ACMG	American College of Medical Genetics and Genomics
*	AD	autosomal dominant
*	AFAP	attenuated FAP
*	AMP	Association for Molecular Pathology
*	AR	autosomal recessive
	array CGH	array comparative genomic hybridization
*	BHD	Birt-Hogg-Dubé
*	BQ	Background Question
*	CAP	College of American Pathologists
	CDC	Centers for Disease Control and Prevention
*	CGP	comprehensive genomic profiling
*	CHIP	clonal hematopoiesis of indeterminate potential
	CHRPE	congenital hypertrophy of the retinal pigmented epithelium
*	ClinGen	Clinical Genome Resource
	CMMRD	constitutional mismatch repair deficiency
	CNV	copy number variation
	COSMIC	Catalogue Of Somatic Mutations In Cancer
	ctDNA	circulating tumor DNA
	dMMR	deficient MMR
	ELSI	Ethical, Legal, Social Issues
*	ESMO	European Society for Medical Oncology
	EUA	examination under general anesthesia
*	EUS	endoscopic ultrasound
*	FAP	familial adenomatous polyposis
*	FQ	Future Research Question
	GAPPS	gastric adenocarcinoma and proximal polyposis of the stomach
*	GIST	gastrointestinal stromal tumor
*	GPV	germline pathogenic variant
*	GRJ	GeneReviews Japan
	GUS	gene of uncertain significance
*	HBOC	hereditary breast and ovarian cancer

	HDGC	hereditary diffuse gastric cancer
*	HGVS	Human Genome Variation Society
*	HLRCC	hereditary leiomyomatosis and renal cell cancer
*	HRD	homologous recombination deficiency
*	HRR	homologous recombination repair
	ICGC	International Cancer Genome Consortium
	IDP	intensive downstaging polypectomy
	IHC	immunohistochemistry
	LAM	lymphangioleiomyomatosis
	MAP	*MUTYH* associated polyposis
*	MGPT	multigene panel testing
*	MINAS	multi-locus inherited neoplasia allele syndrome
	MLPA	multiplex ligation-dependent probe amplification
*	MMR	mismatch repair
	Mondo	Mondo Disease Ontology
*	MRCP	magnetic resonance cholangiopancreatography
*	MSI	microsatellite instability
	MSK-IMPACT	Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets
	NCBI	National Center for Biotechnology Information
*	NCCN	National Comprehensive Cancer Network
*	NGS	next-generation sequencer
	NIH	National Institutes of Health
	NLM	United States National Library of Medicine
	NSGC	National Society of Genetic Counselors
*	OMIM	Online Mendelian Inheritance in Man®
*	PGPV	presumed germline pathogenic variant
	pMMR	proficient MMR
	PPGL	pheochromocytoma/paraganglioma
	PPI	public and patient involvement
*	PRS	polygenic risk score
	RCV	Reference ClinVar record
*	RRM	risk-reducing mastectomy
*	RRSO	risk-reducing salpingo-oophorectomy
	SCTAT	sex cord tumor with annular tubules
	SFWG	secondary findings working group
*	SNV	single nucleotide variant
*	SSGT	syndrome-specific genetic testing

*	SV	structural variation
	SVI	sequence variant interpretation
*	T/N	tumor-normal
*	TMB	tumor mutation burden
*	T-only	tumor only
	VAF	variant allele frequency
*	VCEP	Variant Curation Expert Panels
*	VUS	variant of uncertain significance
*	WES	whole-exome sequencing
*	WGS	whole-genome sequencing
	WTS	whole-transcriptome sequencing

CHAPTER 1. Introduction to hereditary cancer syndromes

Overview 1

Overview of hereditary tumor syndromes

1. Basics of hereditary cancer syndromes

1. Changes in the term

For over 100 years, malignant tumors frequently occur among blood relatives or within families (a phenomenon known as familial clustering[1]). Such cases were historically referred to as 'familial tumors' or 'familial cancers.' Since the 1990s, cancer susceptibility (predisposition) genes responsible for familial tumors have been identified one after another. As a result, the terms "hereditary tumors" or "hereditary cancers" have come to describe tumors or diseases in which cancer susceptibility genes play an established and significant role in tumor development, regardless of familial clustering or inheritance pattern. However, there is no clear distinction between 'familial tumors' and 'hereditary tumors,' and both terms are used in daily medical practice today. With advances in molecular genetic research, the concept of cancer susceptibility genes has become more widely known, and the terms 'hereditary cancer predisposition syndrome' and 'hereditary cancer syndrome' have recently come to be used more frequently than 'hereditary tumors,' especially in overseas countries. That said, expert opinions vary on the differences between these terms, and no clear criteria have been established for their differentiation. In this context, the present guidance defines the term 'hereditary cancer syndrome' as a "syndrome caused by carrying a germline pathogenic variant (GPV) in cancer susceptibility genes," and we consider it a concept that applies regardless of whether cancer has or has not developed.

2. Characteristics of hereditary cancer syndromes

Hereditary cancer syndromes increase an individual's predisposition to developing cancer in multiple, specific organs (Table 1-1), and some affected individuals may also present with non-cancer-related symptoms. Furthermore, cancer susceptibility genes associated with specific organs vary by cancer type. The disease concept of hereditary cancer syndromes also includes the so-called 'cancer-free state' (individuals who have not developed cancer), in which an individual has not developed a disease-associated tumor despite having a causative GPV.

The characteristics of hereditary cancer syndromes observed in the current and past medical history include: (1) cancer onset at a young age (a significantly younger age than the general age of cancer onset), (2) multiple, overlapping, or bilateral cancer, (3) cancer with a distinctive histological type, (4) distinctive physical findings, and (5) rare cancer with low incidence. The characteristics of hereditary cancer syndromes observed in family history include the intrafamilial accumulation of specific cancers. Hereditary cancer syndromes may be anticipated based on the information on the accumulation of specific cancers obtained through interviews on the current/past medical history or family history.

3. Characteristics of genetic information obtained from GPVs (→See BQ6 and BQ9 in Chapter 2)

GPV is present in approximately 10% of cancer patients. GPV provides medical genetic information with the following four characteristics: (1) invariance for the individual, (2) covalency with blood relatives, (3) foreseeability and predictability, and (4) ambiguity (Table 1-2).

4. Classification of genes according to onset risk (→See BQ7 in Chapter 2, as well as Chapter 4)

In hereditary cancer syndromes, both the types of cancer that frequently develop and the risk of cancer onset (penetration rate) vary depending on the specific gene in which a GPV is present.

Cancer susceptibility genes have varying penetration rates, and individuals with hereditary cancer syndromes who carry GPV in cancer susceptibility genes do not necessarily develop cancer (incomplete penetrance). Also, even if genes have the same penetration rate, cancer onset may differ in some organs (cancer types) depending on age or gender. The impact of cancer susceptibility genes on the risk of cancer onset (penetration rate) can be broadly classified into high, moderate, and low degrees of penetrance, and that associated with hereditary breast cancer can be broadly classified into high, moderate, and low risks. Many cancer susceptibility genes with a medium or low degree of penetrance/risk have no established management guidelines.

A large number of hereditary cancer syndromes show a pattern of autosomal dominant (AD) inheritance. Typically, one parent of the affected individual, or a cancer-free carrier, possesses a GPV associated with the hereditary cancer syndrome. In such cases, there is a 50% chance of passing the GPV to offspring. However, if an AD-type GPV arises de novo (as a new mutation), the case may appear sporadic, with no prior family history of the condition.

In carcinogenesis models involving cancer-suppressor genes, pathogenic variants generally occur in one allele in somatic cells first (first hit), followed by the occurrence of pathogenic variants (including the loss of heterozygosity) in the other allele over time (two-hit theory). On the other hand, in carriers of a pathogenic variant in the causative genes of hereditary cancer syndromes associated with cancer-suppressor genes, GPV is present in only one allele, and the first hit is found in all somatic cells from birth. In the other allele, an acquired loss-of-function somatic variant occurs, leading to the development of cancer (Figure 1-1).

The risk of cancer onset for each gene is described in Chapter 4.

Table 1-1. Representative hereditary cancer syndromes, as well as their inheritance pattern, causative cancer susceptibility genes, and tumorous lesions

Disease	Inheritance pattern	Cancer susceptibility genes	Major organs of tumor origin and tumors
Lynch syndrome	AD	*MLH1, MSH2, MSH6, PMS2, EPCAM*	Colorectal cancer, endometrial cancer, gastric cancer, renal pelvis/ureter cancer, ovarian cancer
Familial adenomatous polyposis	AD	*APC*	Colorectal adenoma/carcinoma, gastric adenoma/carcinoma, duodenal adenoma/carcinoma, thyroid cancer, desmoid tumor
MUTYH-related polyposis	AR	*MUTYH*	Colorectal adenoma/carcinoma, duodenal carcinoma
Hereditary diffuse gastric cancer	AD	*CDH1*	Gastric cancer, breast cancer (lobular carcinoma)
Juvenile polyposis syndrome	AD	*SMAD4, BMPR1A*	Gastrointestinal hamartoma, colorectal cancer, gastric cancer
Peutz-Jeghers syndrome	AD	*STK11*	Gastrointestinal hamartoma, gastrointestinal cancer, breast cancer, cervical adenocarcinoma, pancreatic cancer, ovarian tumor, gallbladder cancer, testicular tumor, lung cancer
Cowden syndrome/*PTEN* hamartoma tumor syndrome	AD	*PTEN*	Breast cancer, thyroid tumor, endometrial cancer, colorectal cancer, kidney cancer, gastrointestinal hamartoma
Hereditary breast and ovarian cancer	AD	*BRCA1, BRCA2*	Breast cancer, ovarian cancer, prostate cancer, pancreatic cancer
Li-Fraumeni syndrome	AD	*TP53*	Breast cancer, soft tissue sarcoma/osteosarcoma, brain tumor, adrenocortical cancer
von Hippel-Lindau disease	AD	*VHL*	Central nervous system/retinal hemangioblastoma, kidney cancer, pheochromocytoma/paraganglioma, pancreatic

			tumor, epididymal cystadenoma
Hereditary retinoblastoma	AD	*RB1*	Retinoblastoma, osteosarcoma, soft tissue sarcoma
Tuberous sclerosis	AD	*TSC1*, *TSC2*	Central nervous system tumor, renal angiomyolipoma, pulmonary lymphangioleiomyomatosis, cardiac rhabdomyoma
WT1-related Wilms tumor	AD	*WT1*	Wilms tumor (nephroblastoma)
Multiple endocrine neoplasia type 1	AD	*MEN1*	Parathyroid hyperplasia, pancreatic and gastrointestinal neuroendocrine tumor, pituitary tumor, adrenocortical tumor
Multiple endocrine neoplasia type 2	AD	*RET*	Medullary thyroid carcinoma, pheochromocytoma
Hereditary pheochromocytoma and paraganglioma syndrome	AD	*SDHA, SDHAF2, SDHB, SDHC, SDHD, MAX, TMEM127*	Paraganglioma, pheochromocytoma
Neurofibromatosis type 1	AD	*NF1*	Neurofibromatosis, fibrosarcoma, gastrointestinal stromal tumor, breast cancer
Neurofibromatosis type 2	AD	*NF2*	Acoustic neurilemoma, spinal cord tumor, meningioma

AD: autosomal dominant inheritance, AR: autosomal recessive inheritance
For details on individual genes, see each section in Chapter 4.

Table 1-2. Four characteristics of genetic information[2)]

(1) Invariance	・Genetic information does not change throughout the person's life. ・One round of testing is sufficient for the same gene.
(2) Covalency (heritability and hereditability)	・Some genetic information is shared within the family. ・Identified germline variants are identical among blood relatives. ・Information obtained from one person in the family facilitates testing on blood relatives. ⇒Pre-onset genetic testing, prenatal genetic testing, and pre-implantation genetic testing
(3) Foreseeability and predictability	・Future onset may be predicted in some cases.
(4) Ambiguity	・Judgment on the pathological significance of a variant may change. ・There may be individual differences in the presence or absence of onset predicted from pathogenic variants, timing and symptoms of onset, and severity. ・Clinical utility may change with advances in medicine and medical care.

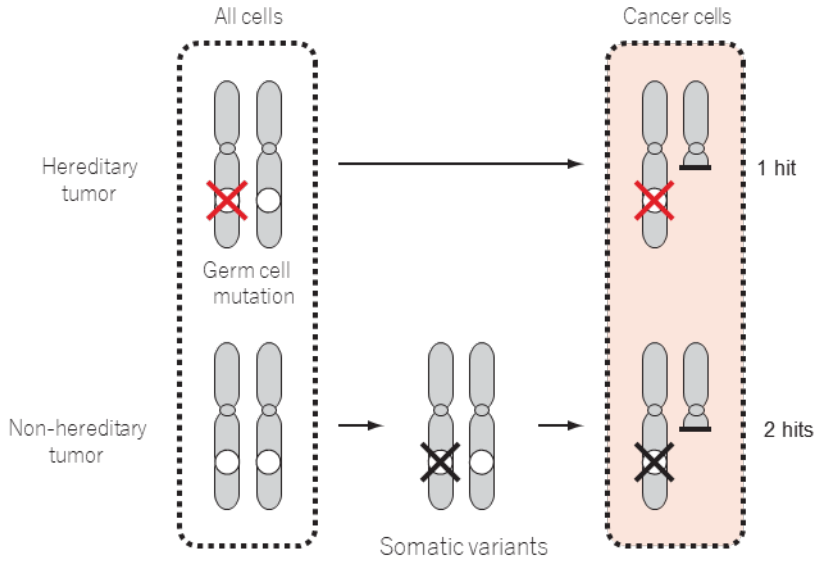


Figure 1-1. Example of two-hit theory in cancer-suppressor genes

2. Genetic testing for individuals suspected of having hereditary cancer syndromes

1. Genetic diagnosis in the proband (→See BQ1, BQ3, and FQ1 in Chapter 2)

With the recent emergence of next-generation sequencers (NGS) technologies, a broader array of genetic testing options is now available for individuals suspected of having hereditary cancer syndromes (Figure 1-2). Such genetic testing can be broadly divided into two types: syndrome-specific genetic testing (SSGT), which analyzes only the genes corresponding to a specific hereditary cancer syndrome, and multigene panel testing (MGPT), which analyzes a large number of genes at once. In Japan, SSGT for some hereditary cancer syndromes is covered by insurance. MGPT, which simultaneously analyzes multiple cancer susceptibility genes, is broadly divided into two types: comprehensive cancer panel (comprehensive MGPT) and cancer-specific panel (cancer-specific MGPT). Other comprehensive genetic testings include whole-exome sequencing (WES) and whole-genome sequencing (WGS). With the development of these testings, SSGT for hereditary cancer syndromes, which is currently implemented in medical practice, may shift to comprehensive analyses, such as MGPT, WES, and WGS, in the future. Additionally, with the use of comprehensive MGPT, WES, WGS, and other genetic tests, GPV with clinical utility may be detected in genes where they are not expected based on the disease phenotype, and responses to such cases are expected to be necessary in the future.

***Side note 1-1**

Comprehensive MGPT usually analyzes a large number of genes (tens to hundreds or more genes).

In cancer-specific MGPT, target genes (around 10 to 20 genes in most cases) are selected based on the risk of cancer onset in each organ. When performing either type of MGPT, each testing company selects the target genes, analysis method, and analysis range based on its own selection criteria. Therefore, options for genetic testing must be thoroughly considered while keeping in mind that they have different criteria.

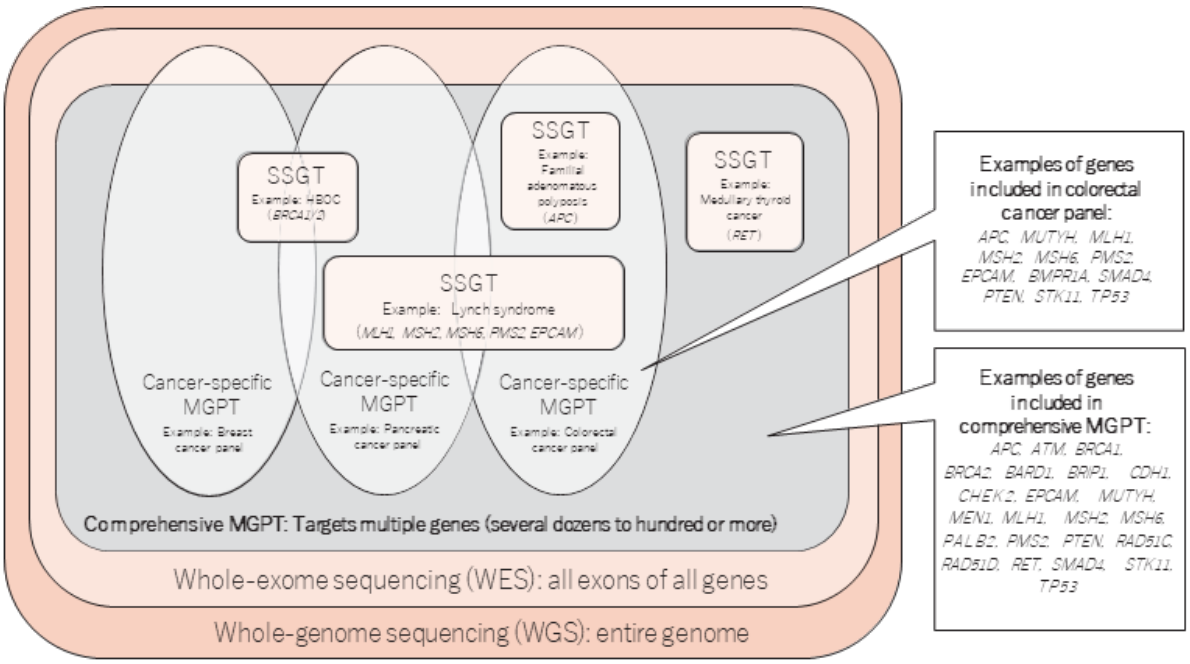


Figure 1-2. Examples of genetic testing for hereditary cancer syndromes

Variants detected by NGS are predominantly single-nucleotide variants (SNVs). Structural variation (SV) is a general term for large structural changes in genes with a size of more than 1 kb, including deletions, duplications, insertions, inversions, translocations, and complex rearrangements. Detection of advanced structural abnormalities, such as SV, may require the use of multiplex ligation-dependent probe amplification (MLPA), array comparative genomic hybridization (array CGH), and other methods in combination. Some genes are known to have pseudogenes, such as *PMS2* and *SDHA*, and it may be difficult to distinguish them during analyses because of the high similarity in their sequences, which often affects the accuracy of variant detection. Therefore, knowing the regions that may be affected by pseudogenes is crucial for understanding the results of MGPT.

2. Germline findings based on the results of comprehensive genomic profiling (CGP) (→See BQ6 in Chapter 2)

Most of the pathogenic variants in cancer-related genes found in tumor tissue occur during tumor cell division. Also, if an individual has GPV in genes associated with hereditary cancer syndromes, the GPV is detected in all cells in the body, including cancer cells. Thus, GPV may be identified or suspected (presumed germline pathogenic variant: PGPV) by comprehensive cancer genome profiling (CGP) testing, although it is positioned as a test for somatic genes in tumor tissue. Such findings are treated as germline findings (so-called 'secondary findings'), and they are distinguished from 'primary findings,' whose identification is the original purpose of CGP. Tumor-only (T-only) CGP, which examines only tumor tissue, identifies PGPV, and testing of specimens other than tumor tissue (blood in many cases) is required to determine whether the individual has a hereditary cancer syndrome.

3. Single-site testing (→See BQ1 and BQ2 in Chapter 2)

Single-site testing is performed for the following two purposes:

(1) To determine if the GPV that has been previously identified in an individual (proband), if any, is also present in blood relatives

(2) To determine whether PGPV detected by CGP is GPV

4. Accuracy management in performing genetic testing (→See BQ8 in Chapter 2)

To improve the accuracy of genetic diagnosis for hereditary cancer syndromes, it is important to ensure the quality and accuracy of specimen testing. In recent years, gene-related testing has become widely used as a clinical test; in Japan, the Act for Partial Revision of the Medical Care Act – Revised Medical Care Act (Act No. 57), which came into effect in December 2018, newly established the classification of "gene-related chromosomal testing" independently within specimen testing, and accuracy control standards and regulations for its implementation have been established.

3. Variants and their interpretation

1. Description of variants (→See Chapter 5)

To describe changes (variants) from the human reference genome (standard genome sequence), the description method set by the Human Genome Variation Society (HGVS) [http://varnomen.hgvs.org/] is commonly used. Typically, variants are described in the order of reference sequence information, positional information, and information on the change. In general, they are often described at the coding DNA (c.) or protein (p.) level.

2. Interpretation of variant pathogenicity (→See BQ5 in Chapter 2)

Because each variant has a different pathogenicity (pathological significance), we must evaluate the pathogenicity of all variants. With recent advances in sequencing technology, an increasing number of genes related to genetic diseases are analyzed, and there has been a dramatic increase in the number of variants detected by testing. In this context, the American College of Medical Genetics and Genomics (ACMG) established a joint working group with the Association for Molecular Pathology (AMP) and the College of American Pathologists (CAP) to develop the 2015 ACMG/AMP guidelines, which include definitions of terms and detailed guides on variant classification.

The 2015 ACMG/AMP guidelines classify variant pathogenicity into the following five categories:

- Pathogenic
- Likely pathogenic
- Variant of uncertain significance (VUS)
- Likely benign
- Benign

The 2015 ACMG/AMP guidelines have been the subject of various discussions since their formulation, and it should be noted that the guidelines have their own characteristics, limitations, and gene-specific evaluation methods.

3. What should be considered when somatic mosaicism is suspected?

Heterozygous GPV usually has a variant allele frequency (VAF) of approximately 50% when analyzed in blood[3].

When VAF is found to be below 50%, the possibility of somatic mosaicism must be considered. In patients who have somatic mosaicism for a single-gene disease with a pattern of AD inheritance, their general clinical symptoms are said to be often milder than in those with a disease caused by the GPV. However, even if a parent has somatic mosaicism, his/her gametes (sperm or eggs) contain a single genetic code, and the child with GPV in the gene will exhibit a clinical course typical of a hereditary cancer syndrome. Also, the identification of somatic mosaicism at a relatively high frequency has been reported for *TSC1/2* and *APC*.

It should also be noted that the variants detected in normal samples include those that are attributed to clonal hematopoiesis of indeterminate potential (CHIP) associated with aging, treatment course, and other factors, especially in *TP53*, *CHEK2*, and *ATM*[8]. In some cases, it can be difficult to distinguish among germline/somatic mosaicism, CHIP, and contamination with circulating tumor DNA (ctDNA) or circulating tumor cells in the blood. Also, it is important to note that when analyzing *TP53*, *CHEK2*, and

ATM variants identified during genetic testing, those attributed to CHIP may be erroneously determined as germline variant.

4. From genetic assessment to management based on genetic information (→See Chapter 4)

Once the presence of GPV is confirmed, an emphasis is placed on the effectiveness (actionability) in health management from a medical perspective, and different management is proposed for each gene.

In Japan and other countries, clinical practice guidelines of response policies for surveillance and reduction in cancer onset risk, including those for cancer-free individuals, have recently begun to be developed for some cancer susceptibility genes. In Japan, an increasing number of clinical practice guidelines related to hereditary cancer syndromes are developed. In overseas countries, such clinical practice guidelines are often developed based on the guidelines created by the U.S. National Comprehensive Cancer Network (NCCN).

Cancer susceptibility genes analyzed in MGPT are divided into two types: (1) those for which there is a certain amount of evidence (such as domestic and international guidelines) and (2) those for which there is insufficient evidence (such as a lack of guidelines or papers with a high level of evidence). Analysis of the degree of tumor development risk may also include genes for which there is insufficient evidence.

In the "List of Secondary Findings in Cancer Gene Panel Testing by Recommendation Level for Patient Disclosure (Ver4.2_20231003)" released by the Secondary Findings Working Group (SFWG) of the Liaison Council for Core Hospitals for Cancer Genome Medicine, a grade is assigned to each gene based on the following: (1) judgment criteria and implementation recommendation levels for conducting confirmatory testing to determine whether PGPV is of germline origin once it is detected by T-only CGP, which examines only tumor tissue, and (2) disclosure recommendation levels from a medical perspective (actionability) upon confirmation of GPV. Regarding the disclosure recommendation levels from a medical perspective (actionability), grade AAA is assigned to genes for which there are treatment policy guidelines for GPV carriers in Japan, or equivalent genes. Grade AA is assigned to genes listed in the NCCN guidelines for which there are disclosure recommendations for surveillance, and those genes correspond to cancer susceptibility genes for which there is a certain amount of evidence.

5. Genetic counseling (→See BQ4 in Chapter 2)

1. What is genetic counseling?

Genetic counseling is considered a process of assisting individuals in understanding and adapting to the medical, psychological, and familial implications of genetic involvement in disease[4]. The process includes (1) interpretation of family and medical history to assess the possibility of disease occurrence and recurrence, (2) education on genetic phenomena, testing, management, prevention, resources, and research, and (3) informed choice (autonomous choice made after obtaining information) and counseling to promote adaptation to risks and circumstances. These follow the definition of the National Society of Genetic Counselors (NSGC)[5]. Genetic counseling is not merely a place to provide information; it is a place to provide psychosocial support that enables clients to make autonomous choices.

2. Genetic counseling for clients suspected of having hereditary tumor syndromes

With the cooperation of related departments and divisions, individuals suspected of having a hereditary tumor syndrome are also provided with necessary information and support, including the following: review and evaluation of the medical status of the patient or client including genetic risk, consideration of risk assessment methods including genetic testing and presentation of options, consideration of risk-based health management in the future and presentation of options, and psychosocial support. When conducting genetic testing, any decision made autonomously by an individual must be respected. Additionally, if an individual or child is unable to express their will, it is desirable that a policy decision that respects the

interests and will of the person is made between medical professionals and the guardian or surrogate and that the informed assent of the child is obtained.

In genetic counseling provided during cancer treatment, it is required to properly evaluate hereditability and provide its information while giving basic psychological considerations. In addition, although genetic information is shared among blood relatives and family members, each individual has a unique understanding, interpretation, thoughts, and ideas about genetic information. Information sharing between the individual diagnosed with a hereditary tumor syndrome and his/her blood relatives is important for the health management of blood relatives. If the blood relative is a child, the information may not need to be shared immediately after the individual's genetic diagnosis, but it should be shared by the age at which medical management is prescribed. Also, time, content, and method of information sharing with children are discussed in genetic counseling. It is natural that people have concerns, fears, and worries about cancer and genetics, and that there are disagreements among family members. It is believed that many people can sort out their feelings and deal with family issues on their own over time. It is important for medical professionals to calmly watch over patients and their families, acknowledge that it is normal for them to be unable to make decisions immediately, and ensure an environment in which they can be comfortable with their worries and anxieties.

Genetics and genetic testing are becoming increasingly involved even in regular cancer treatment, and currently, sufficient time is spent on their practice with the efforts of attending physicians and nurses, such as setting aside time for a separate interview. In fact, rather than focusing on the term 'genetic counseling,' the highest priority should be placed on establishing systems to ensure that the content of genetic counseling is implemented in some form of medical care. However, genetic counseling requires specialized knowledge and time, and it is not easy for attending physicians and current medical staff to carry out the entire process. In Japan, where education and training opportunities in genetic medicine have not been sufficiently developed, physicians and nurses are not always able to respond adequately to medical genetic issues. Therefore, there is a strong need to establish a training system for all medical professionals engaged in cancer treatment to acquire basic knowledge of genetic medicine, as well as to strengthen genetic medicine departments that specialize in genetic counseling and contribute to the practice of comprehensive medical care in appropriate cooperation with physicians and nurses.

***Side note 1-2**

Genetic testing may be performed on pediatric patients if they have developed cancer or have been clinically diagnosed with a hereditary cancer syndrome. In order for the child to adapt to his/her hereditary cancer syndrome, it is important to support both the child and the parents according to the child's age, developmental stage, and level of understanding. For the pre-onset diagnosis of hereditary cancer syndromes for which medical management begins in adulthood or later, it is generally desirable to conduct testing based on the decision made autonomously by the individual, as with genetic testing for other single-gene diseases. (→**See BQ4 in Chapter 2**)

3. Handling of genetic information and data sharing (→See BQ9 in Chapter 2)

Because individuals with hereditary cancer syndromes may develop cancer in multiple organs, their surveillance involves multiple departments. To ensure medical care, the information on GPV obtained through genetic testing must be shared among related medical departments and medical professionals. The

"Guidelines for Genetic Testing and Diagnoses in Medical Care," released by the Japanese Association of Medical Sciences and revised in 2022, also state that, from the perspective of medical safety, all medical information, including the results of genetic testing and genetic information, must be kept in electronic medical records so that they can be shared among medical professionals involved in the patient care, which is necessary for the promotion of team-based medical care. To ensure proper handling of genetic testing information stored in medical records, medical institutions are required to provide medical professionals who have access to genetic information with sufficient education and training on basic knowledge of genetic medicine and matters related to the appropriate handling of personal genetic information. When providing results to other medical institutions, the content and scope of the information to be provided should be considered individually for each case.

In Japan, the "Act on the Comprehensive and Planned Promotion of Measures to Ensure that the Public Can Receive High-quality and Appropriate Genomic Medicine With Peace of Mind" (Act on the Promotion of Genomic Medicine) was enacted and put into effect in June 2023. In order to ensure the effectiveness of the Act and its administrative implementation, a concrete plan for the comprehensive enforcement of genomic medicine policies needs to be formulated.

■ References

1) Warthin AS. Heredity with reference to carcinoma as shown by the study of the cases examined in the pathological laboratory of the University of Michigan 1895-1913. Arch Intern Med. 1913;12(5):546-55.
2) Liaison and Coordination Committee for the Revision of the Model Core Curriculum. Model Core Curriculum for Medical Education (2022 Revised Edition).
https://www.mext.go.jp/content/20240220_mxt_igaku-000028108_01.pdf (accessed 2024-08-26)
3) Truty R, Rojahn S, Ouyang K, et al. Patterns of mosaicism for sequence and copy-number variants discovered through clinical deep sequencing of disease-related genes in one million individuals. Am J Hum Genet. 2023;110(4):551-64. [PMID: 36933558]
4) Japanese Association of Medical Sciences. Guidelines for Genetic Testing and Diagnoses in Medical Care (Revised March 2022). 2022.
https://jams.med.or.jp/guideline/genetics-diagnosis_2022.pdf (reference 2024-08-26)
5) Resta R, Biesecker BB, Bennett RL, et al. A new definition of Genetic Counseling：National Society of Genetic Counselors' Task Force report. J J Genet Couns. 2006;15(2):77-83. [PMID: 16761103]

Overview 2

MGPT for hereditary cancer syndromes

1. Overview of MGPT for hereditary cancer syndromes

1. Targets (→See BQ1 in Chapter 2)

Individuals suspected of having hereditary cancer syndromes include "clients suspected of having a hereditary cancer syndrome based on phenotype," and MGPT is considered for "clients for whom preventive intervention is considered," "clients who require drug susceptibility prediction," and others meeting certain criteria. A diagnosis of a hereditary cancer syndrome by MGPT may lead to appropriate medical intervention, and the targets of MGPT are not necessarily limited to a specific age group or population, regardless of whether they have or have not developed cancer.

2. Significance (→See BQ1 and BQ2 in Chapter 2)

MGPT does not necessarily assume a specific disease; it evaluates the risk of and diagnoses a wide range of hereditary cancer syndromes by analyzing a large number of candidate genes at once. Thus, it may lead to a diagnosis of a hereditary cancer syndrome that has not been suspected based on medical or family history. In genetic testing that analyzes only the genes corresponding to a specific hereditary cancer syndrome (SSGT) (such as *BRCA1/BRCA2* genetic testing for the diagnosis of hereditary breast and ovarian cancer), opportunities for diagnosing hereditary cancer syndromes are likely overlooked in a certain percentage of cases, and MGPT may reduce the number of such cases.

Furthermore, MGPT is expected to contribute to efficient genetic diagnosis at a lower cost and in a shorter period of time than examining cancer susceptibility genes by performing multiple sets of SSGT. In the United States, among the patients with breast and ovarian cancer undergoing genetic testing, the number of those undergoing MGPT has been significantly greater than the number of those undergoing SSGT for *BRCA1/2* since around 2014[1)].

3. Clinical utility (→See BQ3 in Chapter 2)

MGPT can comprehensively evaluate the genetic risk of individuals through the analysis of a wide range of genes, and it is clinically useful as it promotes the provision of precision medicine based on individual genetic risk.

4. Operations and issues (→See BQ3, BQ4, and BQ7 in Chapter 2, as well as Chapters 3 and 4)

Even if there are no domestic or international guidelines for the management of individual cancer susceptibility genes, the diagnosis of hereditary cancer syndromes by MGPT may provide useful information. Diagnosis of hereditary cancer syndromes enables proposals for risk reduction measures and responses for early detection in collaboration with relevant medical departments for each cancer susceptibility gene. On the other hand, if no GPV is detected in the cancer susceptibility genes analyzed by MGPT, unnecessary testing can be avoided, and new risk management tailored to each individual can be proposed. However, it should be noted that there are limitations to the testing and that new information on

the causative genes of hereditary cancer syndromes may be added in the future.

MGPT has some issues, including the increase in VUS, unexpected genetic diagnosis, and the inclusion of cancer susceptibility genes with unclear clinical utility in the analysis. Furthermore, its issues unique to Japan include the lack of MGPT approved by the Pharmaceutical and Medical Device Act (Act on Securing Quality, Efficacy, and Safety of Products Including Pharmaceuticals and Medical Devices) as of August 2024, as well as the cost burden, as it is not covered by health insurance. Genetic diagnosis is not the only purpose of MGPT; there is a need to establish systems in advance, including the subsequent exit strategy, and social implementation in Japan has not kept pace at present. Specifically, even after making a diagnosis of hereditary cancer syndrome and identifying diseases that require attention, there are currently limitations to conducting uniform surveillance in Japan.

5. Establishment of systems at MGPT-implementing facilities (→See BQ9 in Chapter 2, as well as Chapter 5-5 'Model documents')

When newly introducing MGPT, medical institutions must establish the following systems:

(1) Contract with testing company: Each medical institution must understand the type and number of cancer susceptibility genes to be tested, type of MGPT, cost, responses to genetic testing for blood relatives, content of testing report (clarity and language), policy on amended reporting (at what intervals variant evaluations are reviewed and whether an amended report is issued), and other aspects.

(2) Establishment and review of specimen submission process: Each medical institution must create a workflow for sending out specimens for testing.

(3) Preparation of explanatory and consent documents for testing: Each medical institution must prepare necessary documents at its discretion.

(4) Method of result disclosure: Each medical institution must prepare materials to provide information on how to interpret results and manage health in the future

(5) Establishment of surveillance system: Each medical institution must establish a collaboration system with multiple departments and facilities (a system to share updated information with collaborative partners in the future)

Although the required systems vary depending on the size of each institution, medical institutions implementing MGPT are, in principle, expected to establish systems that play a role up to the exit strategy according to the results.

6. Items described in the MGPT report

The content and format of the MGPT report are not standardized among testing companies. Typical items included in the report are listed below (Table 1-3).

Each medical institution should understand the characteristics of each testing company with regard to the items included in the MGPT report and work on appropriate testing operations and management of reports based on the results.

(1) Reporting number: A number used by each testing company to manage outgoing tests

(2) Background information of the patient/medical institution, etc.: When conducting genetic testing, operations that ensure to avoid unintentional switching of client information are essential for medical

safety. The "Guidelines for Genetic Testing and Diagnoses in Medical Care" of the Japanese Association of Medical Sciences were revised in 2022, and their Q&A section clearly stated that it is not mandatory to refrain from writing the individual's name when sending out specimens for testing and required compliance with the Act on the Protection of Personal Information and other laws. When operating without using the individual's name, considerations must be given to avoid unintentional switching of patient information by reviewing multiple pieces of patient information, such as date of birth and gender, as well as specimen information, such as the name of the physician in charge of specimen submission and the date of specimen collection, from the perspective of medical safety.

(3) Information of the specimen: Information of the specimen used in MGPT

(4) Testing results (Table 1-4): Testing results are broadly divided into 'summary of results,' 'details of variants,' 'clinical information,' and 'details of testing method.'

(5) List of genes tested: Cancer susceptibility genes analyzed in MGPT

(6) Disclaimer

(7) Reference literature

(8) Address and contact information of the testing company

Table 1-3. **Example of items included in the MGPT report**

Original text		Supplementary information
Reporting No.		To be used at the testing facility
〈Patient/ordering physician〉		
Patient ID		Some reports contain patient name.
Date of birth		
Gender		
Reason for testing (indication)		Family history, etc.
Ordering physician		
Facility		
〈Sample/specimen〉		
Sample ID		
Sample type (collection site)		Blood, saliva, etc.
Date collected		
Date received (accession)		
Date reported		
〈Testing results〉		
Variant details (summary)	Pathogenic/likely pathogenic variants (Result)	*POSITEVE/NEGATIVE/ UNCERTAIN*
	Genomic alterations (Gene＋variant detected ＋amino acid change)	
	Transcript	NM_xxx, etc.
	Zygosity	hetero/homo
	Classification	pathogenic/likely pathogenic/uncertain significance
Clinical summary	Cancer risk evaluation	
	Management recommendation	
Test details	Methodology	
	Limitation	Regarding NGS
	Database used	
Gene list		
Disclaimer		
References		
Labo		

Table 1-4. Content of the MGPT result report

Summary of results	Some reports state whether the result is positive or negative. In such reports, attention should be paid to the definition of 'positive' and 'negative' results. When multiple variants are detected in a cancer susceptibility gene, the presence of a GPV yields a positive result, even if VUSs are also present. On the other hand, detection of only several VUSs yields a negative result. Thus, the testing results should not be judged based only on the summary result, and details of variants should be thoroughly reviewed.
Details of variants	Details of the variants detected, as well as an evaluation of the pathological significance of the variants by the testing company, are provided.
Clinical information	When the summary result is reported as positive, the report provides the risk of cancer onset in each organ and recommended medical management. In addition, many testing companies include a statement for clients with a positive summary result, encouraging them to share their genetic information with their relatives for the purpose of surveillance.
Details of testing method	The report provides a description of NGS, limitations of the testing, and databases used in the evaluation.

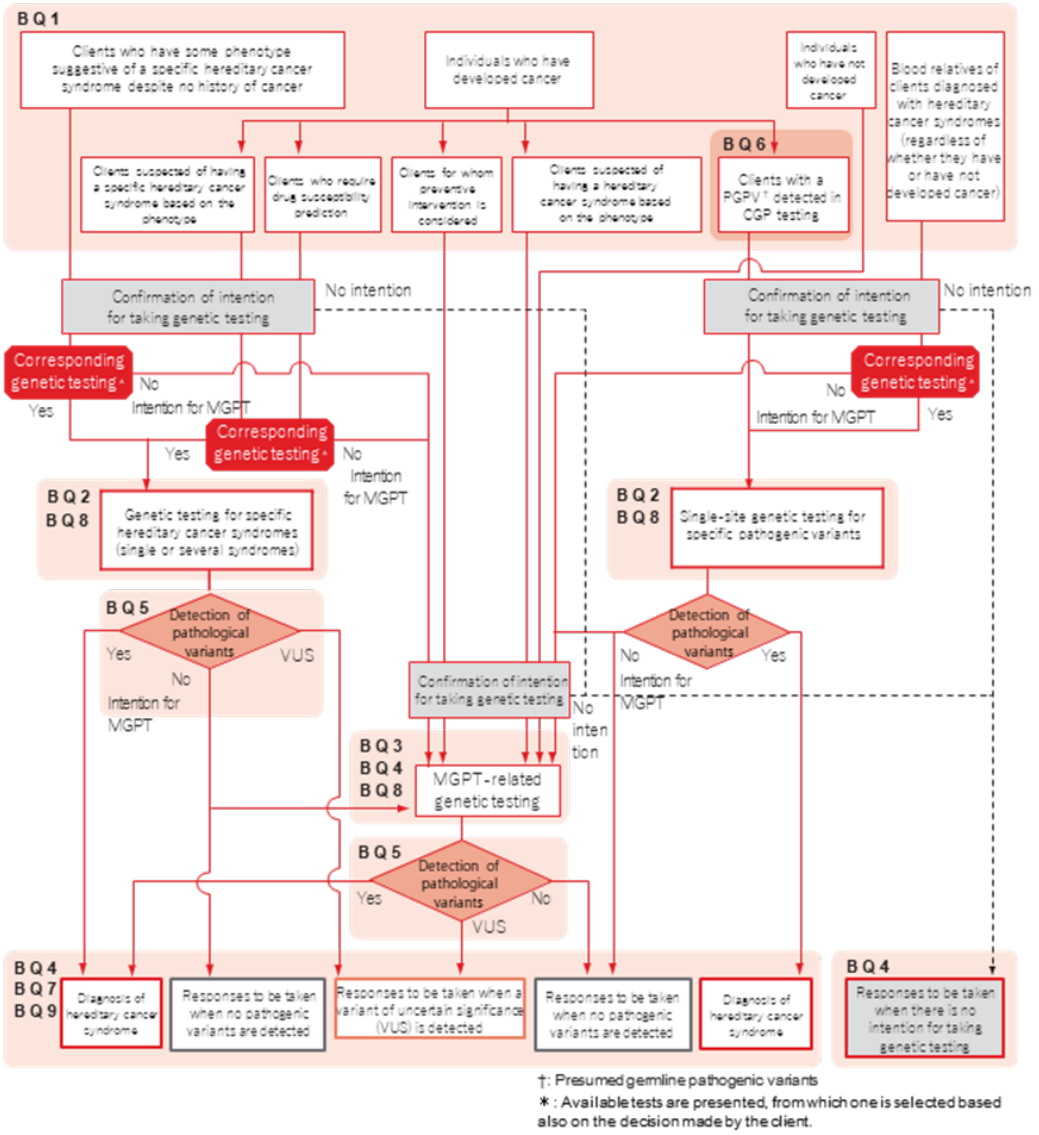
■ Reference

1) Kurian AW, Ward KC, Hamilton AS, et al. Uptake, results, and outcomes of germline multiple-gene sequencing after diagnosis of breast cancer. JAMA Oncol. 2018; 4(8): 1066-72. [PMID: 29801090]

CHAPTER 2. Genetic testing and clinical practice systems for the definitive diagnosis of hereditary cancer syndromes

Clinical algorithm

MGPT and diagnostic algorithm for diagnosing hereditary cancer syndromes



BQ1: Which clients are eligible for MGPT aimed at diagnosing hereditary tumor syndromes?
BQ2: For which clients should we consider providing genetic testing for specific hereditary tumor syndromes?
BQ3: What are the characteristics and clinical utility of MGPT?
BQ4: What should be considered when providing MGPT-related genetic counseling?
BQ5: How do we interpret the pathogenicity of variants?
BQ6: What is the difference between MGPT and tumor tissue-based genetic testing?
BQ7: What responses should be taken when variants are found in genes for which there is insufficient evidence of association with the risk of disease onset?
BQ8: What should be considered when managing the accuracy of genetic testing for hereditary tumor syndromes?
BQ9: What precautions should be taken when handling genetic information?

†: Presumed germline pathogenic variant

*: Available tests are presented, from which one is selected based also on the decision made by the client.

BQ1: Which patients are eligible for MGPT aimed at definitively diagnosing hereditary cancer syndromes?
BQ2: For which patients should we consider providing genetic testing for specific hereditary cancer syndromes?
BQ3: What are the characteristics and clinical utility of MGPT?
BQ4: What should be considered when providing genetic counseling with MGPT?
BQ5: How do we interpret the pathogenicity of variants?
BQ6: What is the difference between MGPT and comprehensive genomic profiling test using tumor tissue?
BQ7: What responses should be taken when variants are found in genes for which there is insufficient evidence of association with the risk of disease onset?
BQ8: What should be considered when managing the accuracy of genetic testing for hereditary cancer syndromes?
BQ9: What precautions should be taken when handling genetic information?

Figure 2-1. MGPT and diagnostic algorithm for diagnosing hereditary cancer syndromes

(See Table 2-2 for insurance coverage status of various genetic tests.)

1

BQ1

Which patients are eligible for MGPT aimed at definitively diagnosing hereditary cancer syndromes?

◎ Statement

MGPT is particularly recommended for patients suspected of having a hereditary cancer syndrome based on their clinical phenotype, for those in whom preventive interventions are being considered, and for patients who may benefit from drug sensitivity prediction. It is also appropriate for biological relatives of individuals diagnosed with a hereditary cancer syndrome, including both cancer-affected and cancer-free relatives.

Importantly, MGPT is not restricted to a specific population. It can be offered to anyone who is willing to undergo testing and fully understands its implications—both the potential benefits and the associated considerations—regardless of whether or not they have a personal history of cancer.

◎ Background

Individuals with the following phenotypes are suspected of having one or more hereditary cancer syndromes, and diagnosis by genetic testing is considered:

- Those with a history of multiple or overlapping cancers
- Those with a history of cancer with a distinctive histological type or genetic instability [microsatellite instability (MSI) or homologous recombination deficiency (HRD)]
- Those with a history of rare cancer
- Those with a history of early-onset cancer
- Those with a familial accumulation of a certain cancer (family history)

Overseas, approaches using MGPT that cover cancer susceptibility genes with various penetration rates have been increasingly employed for the diagnosis of hereditary tumor syndromes in recent years.

◎ Commentary

MGPT is considered to be an efficient genetic testing capable of detecting hereditary cancer syndromes that cannot be predicted by phenotypes, such as medical or family history, regardless of whether or not the person has developed cancer. When performing MGPT, consideration should be given to ensuring that the process from variant detection to result reporting is properly managed and that the testing is carried out in an environment where its accuracy is guaranteed, so that we can examine whether detected variants are risk factors.

1. MGPT-based diagnosis of hereditary cancer syndromes in “cancer-affected individuals with phenotypes suggestive of a family history of hereditary cancer syndromes”

When a cancer-affected individual is suspected of having a hereditary cancer syndrome based on clinical

indicators, such as personal or family medical history, MGPT increases the likelihood of identifying the syndrome. In Japan, large-scale case-control and cohort studies have examined various cancer susceptibility genes across different cancer types. The findings from these studies provide valuable reference data for estimating the detection rate of GPVs through MGPT.[1-11] **(Table 2-1)**.

Table 2-1. Studies analyzing multiple cancer susceptibility genes in cancer patients in Japan

	Target disease	Number of subjects	Cancer-specific or comprehensive MGPT	Number of genes included in the panel	Genes included in the panel	Overall: Detection rate of pathogenic variants (%)	*BRCA1/2*: Detection rate of pathogenic variants (%)
Kaneyasu[1]	*BRCA1/2*-negative familial breast cancer	568	Cancer-specific MGPT	28	*STK11, PTEN, CDH1, NF1, TP53, NBN, ATM, CHEK2, PALB2, BRIP1, BARD1, RAD51C, RAD51D, EPCAM, MLH1, MSH2, MSH6, PMS2, RAD50, XRCC2, RAD51B, MRE11A, FANCC, BLM, FAM175A, RINT1, FANCM, RECQL*	6.6	–
Inagaki-Kawata[2]	Breast cancer	1,995	Cancer-specific MGPT	11	*BRCA1, BRCA2, PALB2, TP53, PTEN, CHEK2, NF1, ATM, CDH1, NBN, STK11*	5.1	3.9
Hirasawa[3]	Ovarian cancer	230	Cancer-specific MGPT	75 or 79	*AKT1, APC, ARID1A, ATM, BARD1, BMPR1A,*	17.8	11.8

					BRAF, BRCA1, BRCA2, BRIP1 , CBLC , CCNE1, CDH1, CDK12, CDK4, CDKN2A, CHEK1, CHEK2, CSMD3, CTNNB1, CUBN, EGFR, EMSY＊, EPCAM, ERBB2, FAM175A, FANCC, FANCL＊, FAT3, FGFR1, FGFR2, GABRA6, GNAS, GREM1, HNF1A, HNF1B, IGF2R, KIT, KRAS, KREMEN1, MAS1L, MLH1, MLH3, MLL2, MLL3, MRE11A, MSH2, MSH3, MSH6, MUTYH, MYC, NBN, NF1, NRAS, PALB2, PIK3CA, PIKR1 , PMS2, POLD1, POLE , PPM1D, PPP2R1A, PTEN, PDGFRA, RAD50, RAD51B ＊,		

					*RAD51C, RAD51D, RAD54L *, RB1, RECQL, SMARCA4, SMAD2, SMAD4, STK11, TGFBR2, TP53, USP16, XRCC2* (*: analysis of 79 genes only)		
Momozawa[4)]	Breast cancer	7,051	Cancer-specific MGPT	11	*BRCA1, BRCA2, PALB2, TP53, PTEN, CHEK2, NF1, ATM, CDH1, NBN, STK11*	5.7	4.2
Momozawa[5)]	Prostate cancer	7,636	Cancer-specific MGPT	8	*BRCA1, BRCA2, HOXB13, PALB2, CHEK2, ATM, NBN, STK11*	5.1	1.3
Fujita[6)]	Colorectal cancer	12,503	Comprehensive MGPT	27	*APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, HOXB13, MLH1, MSH2, SH6, MUTYH, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53*	3.3	0.5
Mizukami[7)]	Pancreatic cancer	1,005	Comprehensive MGPT	27		6.7	3.4

Usui[8]	Gastric cancer	10,426	Comprehensive MGPT	27	*APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53*	3.7	1.3
Sekine[9]	Renal cancer	1,532 (1,283 patients with clear cell cancer and 249 patients with non-clear cell cancer)	Comprehensive MGPT	40	*APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1 , CDC73, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FH, FLCN, HOXB13, MET, MITF, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, SDHA, SDHB, SDHC, SDHD, SMAD4, STK11, TP53,*	4.1 for clear cell cancer and 5.6 for non-clear cell cancer	0.7 for clear cell cancer and 0.4 for non-clear cell cancer

					TSC1, TSC2, VHL		
Okawa[10]	Bile duct cancer	1,292	Comprehensive MGPT	27	*APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53*	5.5	2.1
Sekine[11]	Upper urinary tract epithelial cancer	208	Comprehensive MGPT	27		2.4	1

2. MGPT-based diagnosis of hereditary cancer syndromes in "individuals for the detection of drug susceptibility or medical intervention such as risk-reducing surgery (both cancer-free and cancer-affected individuals)"

A study in the United States reported that MGPT results can influence cancer treatment plans. In this study, universal genetic testing, in which MGPT was performed without taking into consideration the type of cancer or stage of progression, detected GPV in 397 (13.3%) of 2,984 cancer patients, of whom 149 (37.5%) had GPV in high-penetrance genes. Ultimately, 42 patients (1.4% of all patients and 28.2% of patients with GPV in high-penetrance genes) underwent changes to their treatment plans following testing [12]. In another study, GPV that serves as a therapeutic biomarker was identified in 710 (7.8%) of 9,079 patients with advanced recurrent cancer, of whom 289 (3.2%) received drug treatment based on the information[13].

3. MGPT-based diagnosis of hereditary cancer syndromes in "blood relatives of patients with GPV associated with hereditary tumor syndromes (both cancer-free and cancer-affected relatives)"

Even if the proband in a family has been identified with a GPV associated with a hereditary tumor syndrome, MGPT performed on blood relatives may reveal unexpected genetic findings. Compared with targeted testing for a known familial GPV, MGPT offers a broader diagnostic scope and can identify additional hereditary cancer syndromes. This makes MGPT clinically useful for managing the health of individuals who undergo testing. In the United States, a study conducted MGPT (47 genes) on 3,696 cancer-free blood relatives; 6.2% (230/3,696) were found to have a GPV different from that of the

proband, and 2% had GPVs in multiple genes[14].

MGPT may also be used for families with no suspected hereditary cancer syndromes, as well as in local health checkups or health examinations under various legal systems. It is known that a certain percentage of individuals are found to have a hereditary cancer syndrome, according to the "Cancer-Free Individuals With No Family History of Cancer in the Second-Degree Relatives (Control Group in Case-control Study)," which was collected by Biobank Japan and analyzed for multiple cancer susceptibility genes[4,5], as well as the "Community Resident Cohort," which participated in the Tohoku Medical Megabank Project and underwent germline whole-genome analysis[15]. Diagnosing hereditary cancer syndromes can provide valuable information for risk-stratified health management.

■ References

1) Kaneyasu T, Mori S, Yamauchi H, et al. Prevalence of disease-causing genes in Japanese patients with *BRCA1/2-wildtype* hereditary breast and ovarian NPJ Breast Cancer. 2020; 6: 25. [PMID: 32566746].

2) Inagaki-Kawata Y, Yoshida K, Kawaguchi-Sakita N, et al. Genetic and clinical landscape of breast cancers with germline *BRCA1/2* variants. Commun Biol Commun Biol. 2020; 3(1): 578. [PMID: 33067557].

3) Hirasawa A, Imoto I, Naruto T, et al. Prevalence of pathogenic germline variants detected by multigene sequencing in unselected Japanese patients Oncotarget, 2017; 8 (68): 112258-67.

4) Momozawa Y, Iwasaki Y, Parsons MT, et al. Germline pathogenic variants of 11 breast cancer genes in 7,051 Japanese patients and 11,241 controls: Nat. Commun. 2018; 9(1): 4083.[PMID: 30287823].

5) Momozawa Y, Iwasaki Y, Hirata M, et al. Germline Pathogenic Variants in 7636 Japanese Patients With Prostate Cancer and 12 366 Controls. J Natl Cancer Inst. 2020; 112(4): 369-76. [PMID: 31214711].

6) Fujita M, Liu X, Iwasaki Y, et al. Population-based Screening for Hereditary Colorectal Cancer Variants in Japan. Clin Gastroenterol Hepatol. 2020; PMID: 33309985] (in Japanese)

7) Mizukami K, Iwasaki Y, Kawakami E, et al. Genetic characterization of pancreatic cancer patients and prediction of carrier status of germline EBioMedicine. 2020;60:103033. [PMID: 32980694].

8) Usui Y, Taniyama Y, Endo M, et al. Helicobacter pylori, Homologous-Recombination Genes, and Gastric Cancer. N Engl J Med. 2023;388(13):1181-90. PMID: 36988593]

9) Sekine Y, Iwasaki Y, Aoi T, et al. Different risk genes contribute to clear cell and non-clear cell renal cell carcinoma in 1532 Japanese patients and Hum Mol Genet. 2022;31(12):1962-9.

10) Okawa Y, Iwasaki Y, Johnson TA, et al. Hereditary cancer variants and homologous recombination deficiency in biliary tract cancer. J Hepatol. 2023; J Hepatol. 2023; 78(2): 333-42. [PMID: 36243179].

11) Sekine Y, Iwasaki Y, Hakozaki N, et al. Prevalence and risk estimation of cancer-predisposing genes for upper urinary tract urothelial carcinoma in Jpn J Clin Oncol. 2022;52(12):1441-5. [PMID: 36093724].

12) Samadder NJ, Riegert-Johnson D, Boardman L, et al. Comparison of Universal Genetic Testing vs Guideline-Directed Targeted Testing for Patients JAMA Oncol. 2021;7(2):230-7. [PMID: 33126242].

(13) Stadler ZK, Maio A, Chakravarty D, et al. Therapeutic Implications of Germline Testing in Patients With Advanced Cancers. J Clin Oncol. 2021;39(24): PMID: 34133209]

14) Heald B, Pirzadeh-Miller S, Ellsworth RE, et al. Cascade testing for hereditary cancer: comprehensive multigene panels identify unexpected J Natl Cancer Inst. 2024;116(2):334-7. [PMID: 37756683].

15) Yamaguchi-Kabata Y, Yasuda J, Tanabe O, et al. Evaluation of reported pathogenic variants and their frequencies in a Japanese population based on a J Hum Genet. 2018;63(2):213-30.[PMID: 29192238].

BQ2

For which patients should we consider providing genetic testing for specific hereditary cancer syndromes?

◎ Statement

Genetic testing specific to a hereditary cancer syndrome (syndrome-specific genetic testing (SSGT)) should be considered for (1) individuals suspected of having a specific hereditary cancer syndrome based on the phenotype and (2) individuals requiring a diagnosis of a specific hereditary cancer syndrome to determine a cancer treatment plan (e.g., companion diagnostics).

◎ Background

Diagnosis of a hereditary cancer syndrome is an important indicator for cancer preventive medicine and the selection of cancer treatment drugs. In Japan, some genetic testings are covered by insurance[1]. As preemptive and personalized medicine continues to advance, the demand for genetic testing is expected to grow further. With the ongoing development of medical genetics infrastructure, MGPT is also anticipated to become a more widely considered testing option. However, at present, single- or small-scale gene testing (SSGT) is often preferred for diagnosing specific hereditary cancer syndromes due to factors such as insurance coverage, relevance to companion diagnostics, cost considerations, and clinical practicality.

◎ Commentary

Individuals undergoing SSGT can generally be categorized into two groups: (1) those suspected of having a specific hereditary cancer syndrome based on their phenotype, and (2) those currently receiving cancer treatment for whom the diagnosis of a hereditary cancer syndrome may influence their treatment plan. In clinical practice, suspicion of a hereditary cancer syndrome can arise under various circumstances. A patient may raise concerns based on their personal or family medical history, or a healthcare provider may identify signs suggestive of a hereditary syndrome during routine care, even outside the context of cancer screening or treatment.

To ensure appropriate care and management, medical professionals should possess a fundamental understanding of genetics. When warranted, and in alignment with the patient's preferences, referral to a genetic specialist or genetic counselor should be considered.

1. Individuals suspected of having a specific hereditary cancer syndrome

A specific hereditary cancer syndrome may be clinically diagnosed when clinical findings specific to the

syndrome are found with no or little possibility of other hereditary tumor syndromes based on a detailed interview on the current/past medical or family history. Clinical diagnostic criteria are often determined based on the itemization of multiple clinical findings and the number of relevant items. Diagnosis by genetic testing should also be considered, as genetic diagnosis may provide more reliable information for patients and their blood relatives, including accurate assessment of disease onset risk and provision of surveillance. In such cases, SSGT of the putative causative gene is performed to determine the presence or absence of GPV.

If an individual exhibits a phenotype suggestive of multiple hereditary cancer syndromes, information should be provided regarding MGPT as a testing option. Clinical diagnostic items for a specific hereditary cancer syndrome, as well as indications for genetic testing, can be used as references if they are described in clinical practice guidelines for each cancer type or hereditary cancer syndrome. With the recent promotion of cancer genome medicine in Japan, some gene-related testings can lead to the diagnosis of specific hereditary cancer syndromes. Among those, insurance-covered tests are shown in the table below (Table 2-2).

Table 2-2. Hereditary cancer syndrome-related testings that are covered by insurance in Japan (as of August 2024)

Cancer type, etc.	Target	Purpose	Test/target gene	Company	Insurance points in Japan	Specimen	Start year
Breast cancer	Metastatic recurrent breast cancer	Companion diagnostics (olaparib/talazoparib)	BRACAnalysis® Diagnostic System	Myriad	20,200	Blood	2018 / 2024
	Recurrent high-risk breast cancer	Companion diagnostics (olaparib)	BRACAnalysis® Diagnostic System	Myriad	20,200	Blood	2022
	Breast cancer with a suspicion of HBOC	Diagnosis, selection of surgical procedure, preventive medicine	BRACAnalysis® Diagnostic System	Myriad	20,200	Blood	2020
Ovarian cancer	Advanced ovarian cancer	Companion diagnostics (olaparib)	BRACAnalysis® Diagnostic System	Myriad	20,200	Blood	2019
			FoundationOne® CDx Cancer Genome Profile	FMI	44,000	Tissue	2019
		Companion diagnostics (niraparib)	MyChoice® Diagnostic System	Myriad	32,200	Tissue	2020
	Advanced recurrent ovarian cancer		MyChoice® Diagnostic System	Myriad	32,200	Tissue	2020
	Ovarian cancer	Diagnosis, selection of surgical procedure, preventive medicine	BRACAnalysis® Diagnostic system	Myriad	20,200	Blood	2020
Prostate cancer	Metastatic prostate cancer	Companion diagnostics (olaparib)	BRACAnalysis® Diagnostic System	Myriad	20,200	Blood	2021
			FoundationOne® Liquid CDx	FMI	44,000	Blood	

		Companion diagnostics (olaparib/talazoparib)	FoundationOne® CDx Cancer Genome Profile	FMI	44,000	Tissue	2021 / 2024
Pancreatic cancer	Unresectable pancreatic cancer	Companion diagnostic (olaparib)	BRACAnalysis® Diagnostic System	Myriad	20,200	Blood	2021
Colorectal cancer	Colorectal cancer	Companion diagnostics (nivolumab)	Microsatellite instability testing	Multiple companies	2,500	Tissue	2020
			FoundationOne® CDx Cancer Genome Profile	FMI	44,000		
			Guardant360® CDx Cancer Gene Panel	GH		Blood	2023
		Companion diagnostics (pembrolizumab)	Microsatellite instability testing	Nichirei	2,500	Tissue	2022
		Lynch syndrome screening	Immunohistochemistry of mismatch repair proteins	Roche	2,700	Tissue	2022
Thyroid cancer	Medullary thyroid cancer	Diagnosis, selection of surgical procedure, preventive medicine	*RET*	Multiple companies	5,000	Blood	2016
Retinoblastoma	Retinoblastoma	Diagnosis, selection of surgical procedure, preventive medicine	*RB1*	Multiple companies	5,000	Blood	2016
Solid cancer	Solid cancer	Companion diagnostics (pembrolizumab)	Microsatellite instability testing	FALCO	2,500	Tissue	2018
			Immunohistochemistry of mismatch repair proteins	Roche	2,700		2022
			FoundationOne® CDx Cancer Genome Profile	FMI	44,000		2019
			Guardant360® CDx Cancer Gene Panel	GH		Blood	2023
		Lynch syndrome screening	Microsatellite instability testing	FALCO	2,500	Tissue	2020
				Multiple companies	2,100		2006
MEN1-related tumor	Suspected *MEN1*	Diagnosis, selection of surgical procedure, preventive medicine	*MEN1*	Multiple companies	5,000	Blood	2020
Tuberous sclerosis	Suspected tuberous sclerosis	Diagnosis	*TSC1, TSC2*	Multiple companies	3,880	Blood	2022
Neurofibromatosis	Suspected neurofibromatosis	Diagnosis	*NF1, NF2*	Kazusa	3,880	Blood	2024

□ Blood (germline) testing. ▨ Testing of tumor tissue or circulating tumor DNA in blood.
Myriad: Myriad Genetics Inc., FMI: Foundation Medicine Inc., GH: Guardant Health Inc., Nichirei: Nichirei Biosciences Inc., FALCO: Falco Biosystems Ltd., Kazusa: Kazusa Genetic Testing Laboratory.

If a family member has been diagnosed with a hereditary cancer syndrome and a known GPV, their blood

relatives are also eligible for genetic testing to assess their risk for the same condition. In such cases, single-site analysis, which targets only the variant identified in the proband, can be conducted using detailed genetic information obtained from the proband's test. Since the cost of testing differs between SSGT and single-site analysis, it is important to consider whether relevant genetic information is already available within the family.

When a blood relative with cancer, that is, a relevant phenotype, is considered for genetic testing, they may qualify for insurance-covered SSGT. This decision should be made through a comprehensive evaluation of several factors, including the clinical need for testing, for example, whether companion diagnostics are indicated, associated costs, family history, overall medical burden, and the individual's values and preferences. Additionally, MGPT may be appropriate if the blood relative is suspected of having a hereditary cancer syndrome that differs from the one identified in the proband.

2. Individuals undergoing cancer treatment who require a diagnosis of a hereditary cancer syndrome to determine a treatment plan

For patients undergoing cancer treatment, physicians in charge of cancer treatment often consider genetic testing and provide them with a detailed explanation about the testing. In particular, as of 2024, *BRCA1/2* genetic testing is widely performed by physicians in charge of cancer treatment, as it is covered by insurance and influences treatment plans. Even if the testing is aimed at deciding a treatment plan, an examination by a specialist familiar with genetic medicine or genetic counseling should be considered when a specific hereditary cancer syndrome is suspected. Even when genetic testing is conducted to determine the suitability of a specific therapeutic agent or surgical approach, it is important to inform the patient and their family in advance that, if a GPV is detected, consultation with a specialist in genetic medicine will be necessary. This consultation should include a discussion of future management not only for the patient but also for their blood relatives.

Companion diagnostics is genetic testing commonly performed in cancer treatment settings (Table 2-2). Specimens submitted for companion diagnostics include non-tumor tissue [leukocyte cells from the blood (of an individual without hematopoietic tumor) if the individual has not undergone a bone marrow transplant] and tumor tissue. When using non-tumor tissue, detection of a pathogenic variant by the testing leads to a diagnosis of a hereditary cancer syndrome. When using tumor tissue, SSGT or single-site analysis is often performed to determine whether the variant detected is of germline origin, as its detection only suggests the possibility of a hereditary cancer syndrome.

■ Reference

1) The Japan Society of Human Genetics. Genetic tests covered by insurance.
http://www.kentaikensa.jp/ (reference 2024-08-26)

BQ3

What are the characteristics and clinical utility of MGPT?

◎ Statement

Because MGPT targets a broad range of cancer susceptibility genes, it is characterized by a higher diagnostic yield for hereditary cancer syndromes. At the same time, it is also associated with a relatively high rate of detecting variants of uncertain significance (VUS).

MGPT has substantial clinical utility, as its ability to identify hereditary cancer syndromes can facilitate appropriate risk management for GPV carriers and expand opportunities for tailored cancer treatment. However, caution is warranted, as MGPT often detects VUS and includes genes for which the clinical implications remain unclear.

◎ Background

It has been conventionally believed that 10% of all cancers are hereditary[1], and with the growing use of MGPT, an increasing number of reports supporting this belief are being published. According to a study on MGPT conducted in a population without selection bias regarding cancer history, the detection rate of GPVs in cancer susceptibility genes ranged from 5.5% to 17.5%, with approximately 10% of individuals found to carry a GPV. Specifically, the detection rate was 9.7% to 17.5% in cancer patients and 4.7% to 10.2% in cancer-free individuals.[2-6]. Also, a large proportion of the GPVs identified were in homologous recombination repair (HRR)-related genes or DNA mismatch repair (MMR) genes. Overseas, MGPT has become the mainstream testing for the diagnosis of hereditary cancer syndromes.

◎ Commentary

MGPT, genetic testing that collectively analyzes multiple cancer susceptibility genes, is broadly classified into two types: cancer-specific MGPT (cancer-specific panel) and comprehensive MGPT (comprehensive cancer panel).

Cancer-specific MGPT covers multiple genes associated with the onset risk of a specific cancer, with representative examples including the breast cancer panel and the colorectal cancer panel. Although the genes included vary depending on the testing company, the NCCN guidelines state that genes related to colorectal cancer risk, for example, should include at least *APC, MUTYH, MLH1, MSH2, MSH6, PMS2, BMPR1A, SMAD4, PTEN, STK11, and TP53*[1]. Thus, the type of MGPT should be selected according to the clinical background of the client.

Comprehensive MGPT extensively analyzes cancer susceptibility genes, and the number of genes included varies from 20 to over 100. An increase in the number of genes to be analyzed with MGPT does not lead to the detection of a number of GPVs, on the other hand, the detection rate of VUS increases in proportion to the number of genes analyzed[2].

Cancer susceptibility genes included in MGPT are commonly classified by their degree of penetrance, such as high, moderate, or low, or by their associated level of cancer risk, including high risk (greater than 4 times the absolute risk), moderate risk (2 to 4 times), and low risk (less than 2 times). The latter

classification is often preferred because it conveys risk in quantitative terms. However, it is important to note that these classifications were originally developed in the context of breast cancer–related genes and may not be applicable to all cancer types. Additionally, regardless of the number of genes analyzed, MGPT often includes genes for which the clinical utility has not yet been established.

The table below describes in detail the characteristics and cautions of MGPT in comparison to SSGT and single-site analysis (Table 2-3).

Table 2-3. Characteristics of MGPT in comparison to SSGT and single-site analysis

	Multigene panel testing (MGPT)	Genetic testing for a specific hereditary tumor syndrome (syndrome-specific genetic testing: SSGT)	Genetic testing for a specific site only (single-site analysis)
Concept	MGPT simultaneously examines multiple genes associated with the risk of cancer onset (cancer-specific or comprehensive MGPT).	SSGT examines genes predicted based on cancer type, family history, etc.	Single-site analysis examines the presence or absence of specific variants in genes.
Analysis target	A large number of genes (from several dozens to more than a hundred genes)	One to several genes	Specific variants in genes (There is no limit to the number of genes.)
Properties	・MGPT analyzes a large number of cancer susceptibility genes simultaneously.	・SSGT analyzes the causative genes of a specific hereditary tumor syndrome.	・Single-site analysis examines the presence or absence of variants detected by other tests (e.g., cancer genome profiling testing) or genetic testing of blood relatives.
Characteristics	・MGPT can simultaneously evaluate a large number of hereditary tumor syndromes, improving the detection rate of GPV in the following cases: (a) GPV in phenotype-matched genes (b) GPV in non-phenotype-matched genes (c) GPV in two or more genes (d) GPV that provides useful information for cancer treatment (e) GPV in the causative genes of autosomal recessive diseases (depending on the genes included in MGPT) (f) GPV in genes for which the association with the risk of cancer onset and the management guidance are unclear ・MGPT is not covered by insurance (as of August 2024) (g). ・MGPT is less expensive than performing a set of tests for a single gene, with a shorter time to obtain results. ・If no pathogenic variants are identified, there is no basis for conducting additional genetic	・SSGT can diagnose specific hereditary tumor syndromes with high clinical importance. ・SSGT is relatively inexpensive due to its limited coverage of the analysis region.	・Single-site analysis can diagnose specific hereditary tumor syndromes with high clinical importance. ・Single-site analysis, when performed, has high prior probability. ・Single-site analysis is inexpensive as it analyzes a specific region. ・Short TAT

	testing beyond what is necessary.		
Aspects that require caution when analyzing results	・High detection rate of VUS (high possibility of obtaining ambiguous testing results) (h) ・Accuracy of structural variation (SV) detection (i) ・The analysis target region in each gene differs depending on the testing company.	・SSGT does not yield genetic information outside a specific hereditary tumor syndrome. ・When there are other hereditary tumor syndromes exhibiting a similar phenotype, additional testing may be needed, which is costly and time-consuming.	Because single-site analysis does not analyze regions other than a specific site, hereditary tumor syndromes cannot be ruled out by a negative result or the absence of the variant analyzed.

[The items (a) to (i) in the table are discussed in the main text.]

1. High detection rate of GPV

1. GPV in phenotype-matched genes (a) and non-phenotype-matched genes (b)

Since MGPT analyzes a large number of genes simultaneously, it has a high detection rate of GPV and is more efficient diagnostic testing than syndrome-specific genetic testing (SSGT).

The diagnostic efficiency of MGPT is often demonstrated through its comparison with that of target genetic testing (a method of narrowing down target genes or test recipients through screening based on the NCCN guidelines and other criteria). A study on MGPT in cancer patients with no selection bias, including cancer type, advanced stage, or age at diagnosis, showed that approximately 30% of GPV carriers were not eligible for target genetic testing or had GPV detected in a gene different from that predicted by the phenotype, which accounted for 3.9–6.4% of all individuals who underwent the testing[4-7]. Furthermore, a study of 165,000 patients undergoing MGPT examined a cohort that met only the criteria for *BRCA1/2* testing, reporting that 67% of GPVs detected were in genes other than *BRCA1/2* and that 5.2% were in MMR genes causative of Lynch syndrome. The study also examined patients who met only the criteria for Lynch syndrome testing and found that more than half (53.8%) of the detected GPVs were in non-MMR genes, including *BRCA1/2* (8.8%)[8], highlighting the limitations of targeted genetic testing.

2. GPV in two or more genes (c)

MGPT may reveal GPV in multiple genes. The presence of GPV in two or more cancer susceptibility genes has been termed as 'multi-locus inherited neoplasia allele syndrome (MINAS)' by Whitworth et al.[9]. GPV is known to be identified in both *BRCA1* and *BRCA2* genes, with a reported frequency of 0.8% (2 patients) in 240 Japanese patients with *BRCA1/2* pathogenic variants[10] and 0.3% in 32,295 HBOC women[11].

With the growing use of MGPT, the number of reported MINAS cases has been gradually increasing since 2016. According to reports on MGPT in over 10,000 patients (including cancer-free patients), approximately 3% of GPV carriers have MINAS[4, 7, 8, 12]. In addition, the most common gene combinations were those containing *BRCA1* or *BRCA2*, accounting for 71.4–74.5%[13, 14]. A study reported that pathogenic variants in *BRCA1/2* were found in 88 of 1,156 individuals at high risk of hereditary breast cancer, of whom 10 had MINAS[14]. Also, approximately 11% of individuals with hereditary breast or ovarian cancer had GPV in genes other than *BRCA1/2*, indicating that SSGT for *BRCA1/2* alone may not be sufficient for the diagnosis of hereditary cancer syndromes. A study of 11 breast cancer susceptibility genes identified MINAS in 3 of 7,051 Japanese female patients with breast cancer[15].

Problems that arise in clinical responses include whether MINAS influences the phenotype (age of onset or severity) and whether it has an additive or synergistic effect, but these remain unclear due to little data

available. At present, it is considered appropriate to take the recommended measures for each GPV detected.

3. Possibility that GPV may provide useful information for cancer treatment (d)

Many GPVs detected by MGPT are in cancer susceptibility genes related to HRR or MMR. It is known that homologous recombination deficiency (HRD) serves as a factor predicting the effectiveness of PARP inhibitors and platinum drug sensitivity, while deficient MMR (dMMR), which occurs frequently in tumors of individuals with Lynch syndrome, serves as a factor predicting the effectiveness of immune checkpoint inhibitors. Thus, the presence of GPV in cancer susceptibility genes may be a useful biomarker for drug selection in cancer treatment. However, it should be noted that if the testing is not covered by insurance, information obtained from its results cannot be used immediately for treatment selection.

Of the 84,297 clinical trials registered since 1990, 887 trials (1.1%) used GPV as a biomarker, and the most commonly studied genes were *BRCA2* (228 studies; 25.7%) and *BRCA1* (224 studies; 25.3%). Many trials used HRR-related biomarkers, and commonly studied genes other than *BRCA1/2* were HRD-related genes (regardless of the measurement method) (80 studies; 9.0%), followed by *PALB2* (59 studies; 6.7%) and *ATM* (55 studies; 6.2%)[16].

Individuals with GPV in *ATM* or *CHEK2*, which are HRR-related genes frequently detected by MGPT, may not exhibit the same level of response to PARP inhibitors as those with GPV in *BRCA1/2*[17], but their GPV could provide key information at least for future clinical trials.

Approximately 10% of cancer patients carry GPV in cancer susceptibility genes, which could be used as a predictive factor of treatment efficacy, and a certain percentage of patients have GPV in genes that are not associated with the phenotype. Given these, MGPT performed at the time of cancer diagnosis may provide useful information for subsequent treatment strategies. However, separate companion diagnostics may be needed for drug administration **(→See BQ2)**.

4. GPV in the causative genes of autosomal recessive disease (ARD) (e): Diagnosis of ARD carriers

MGPT often covers multiple causative genes of ARD, some of which increase the risk of cancer onset when GPV is present in the heterozygous state. For example, the presence of GPV in *BRCA1/2* and other genes in the heterozygous state increases the risk of cancer onset, causing serious conditions, such as Fanconi anemia. On the other hand, the presence of GPV in *MUTYH* and other genes in the homozygous state causes *MUTYH*-associated polyposis (MAP), while there is no clear evidence for its effect on the risk of cancer onset in the heterozygous state. The carriers of such GPV are ARD carriers (individuals with such GPV may pass it on to the next generation, although they are unlikely to develop the disease caused by the GPV in the future), and the NCCN guidelines state that genetic counseling regarding these genes should also cover reproductive issues[18].

5. GPV in genes for which the association with the risk of cancer onset and the management guidance are unclear (f)

Because MGPT covers genes for which evidence of management guidance is unclear, it has an issue of clinical utility. The NCCN guidelines[18], which are often used as a reference for genes lacking domestic guidelines and guidance, describe 20 genes with a high to moderate risk, but these include genes for which no recommended medical management has been established and genes that are not suited to the medical situation in Japan. Thus, those performing MGPT should be proficient with its characteristics and limitations. Also, MGPT should ideally be performed by a person with expertise in genetics, and genetic

counseling should be provided before and after the testing[1]. For the provision of risk management, it is desirable to collect the latest evidence and discuss policies with relevant departments.

2. Aspects that require caution when analyzing results

1. High detection rate of variants of uncertain significance (VUS) (h)

MGPT examines a larger number of genes than SSGT, which increases the number of VUSs detected[2, 19, 20]. Because the populations and the number of genes analyzed are not consistent, it is difficult to identify the exact frequency of detecting VUS, but past studies have indicated that MGPT detects VUS at a frequency of approximately 30%, with an average median of 32.6% (10.5–47.4%)[6-8, 19, 21-23].

Also, there are known to be racial differences in the frequency of detecting VUS; the frequency is higher in the non-white population than in the white population, and among the non-white population, Asians have the highest frequency[2]. This is likely due to differences in the populations that are included in the reference database used to determine variant pathogenicity.

2. Accuracy of structural variation (SV) detection (i)

SV, which refers to changes in DNA regions with a size of approximately 1 kb or more, is a general term for major genetic changes, including inversions, balanced translocations, and genomic imbalances [insertions and deletions: commonly referred to as copy number variations (CNV)]. If an SV causes a change in gene expression level or function, it may be classified as GPV. Approximately 7–10% of GPVs in cancer susceptibility genes detected by MGPT are said to be such higher-order structural abnormalities[24-26]. On the other hand, MGPT may not have a high capacity to detect higher-order structural abnormalities, such as SV, depending on the type selected. In such cases, multiplex ligation-dependent probe amplification (MLPA) or array comparative genomic hybridization (CGH) needs to be used in combination to make a judgment, but the method of SV analysis differs depending on the testing company.

Also, the proportion of SVs in the GPVs detected is known to differ depending on the gene; genes with a high frequency of SV include *STK11*, *EPCAM-MSH2*, *BMPR1A*, *PMS2*, *RAD51C*, *CDKN2A*, *CDH1*, and *BRCA1*, and it has been shown that SVs account for more than 10% of GPVs in these genes. When performing MGPT, it is important to be aware that some genes may yield false-negative results due to the lack of sufficient analysis of SVs.

3. Others

1. Insurance coverage (g)

As of August 2024, MGPT is not covered by insurance in Japan. Furthermore, treatment using the results of MGPT for medical management, such as surveillance and risk-reducing surgery, may not be covered by insurance for both the patient and blood relatives. Also, there are a limited number of medical institutions capable of providing genetic medical care, including costs and uninsured care.

4. Clinical utility of MGPT

1. Simultaneous analysis of multiple genes

MGPT covers and analyzes a wide range of genes simultaneously, enabling a comprehensive assessment of an individual's risk for cancer susceptibility and improving the diagnostic rate of hereditary cancer

syndromes. Identification of individuals with GPV can facilitate effective surveillance and measures to reduce the risk of cancer onset. Additionally, MGPT is more efficient than SSGT as it can analyze a large number of genes simultaneously, saving time and money.

2. Promotion of personalized prevention

Based on each genetic risk of GPV carriers, primary and secondary cancer prevention strategies can be selected, such as individualized surveillance and risk reduction methods.

Overseas, MGPT is becoming mainstream since it is more practical than sequential SSGT in terms of diagnostic efficiency, cost, and clinical utility. Thus, in Japan, the clinical implementation of MGPT has become an urgent issue to be addressed.

■ References

1) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Colorectal. Version 2, 2023. (accessed 2024-08-26)
2) Caswell-Jin JL, Gupta T, Hall E, et al. Racial/ethnic differences in multiple-gene sequencing results for hereditary cancer risk. Genet Med. 2018;20(2):234-9. [PMID: 28749474]
3) Easton DF, Pharoah PD, Antoniou AC, et al. Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med. 2015;372(23):2243-57. [PMID: 26014596]
4) Neben CL, Zimmer AD, Stedden W, et al. Multi-Gene Panel Testing of 23,179 Individuals for Hereditary Cancer Risk Identifies Pathogenic Variant Carriers Missed by Current Genetic Testing Guidelines. J Mol Diagn. 2019;21(4):646-57. [PMID: 31201024]
5) Mandelker D, Zhang L, Kemel Y, et al. Mutation Detection in Patients With Advanced Cancer by Universal Sequencing of Cancer-Related Genes in Tumor and Normal DNA vs Guideline-Based Germline Testing. JAMA. 2017;318(9):825-35. [PMID: 28873162]
6) Samadder NJ, Riegert-Johnson D, Boardman L, et al. Comparison of Universal Genetic Testing vs Guideline-Directed Targeted Testing for Patients With Hereditary Cancer Syndrome. JAMA oncol 2021;7(2):230-7. [PMID: 33126242]
7) Rosenthal ET, Bernhisel R, Brown K, et al. Clinical testing with a panel of 25 genes associated with increased cancer risk results in a significant increase in clinically significant findings across a broad range of cancer histories. Cancer Genet. 2017;218-9:58-68. [PMID: 29153097]
8) LaDuca H, Polley EC, Yussuf A, et al. A clinical guide to hereditary cancer panel testing:evaluation of gene-specific cancer associations and sensitivity of genetic testing criteria in a cohort of 165,000 high-risk patients. Genet Med. 2020;22(2):407-15. [PMID: 31406321]
9) Whitworth J, Skytte AB, Sunde L, et al. Multilocus Inherited Neoplasia Alleles Syndrome: A Case Series and Review. AMA Oncol. 2016;2(3):373-9. [PMID: 26659639]

10) Arai M, Yokoyama S, Watanabe C, et al. Genetic and clinical characteristics in Japanese hereditary breast and ovarian cancer:first report after establishment of HBOC registration system in Japan. J Hum Genet. 2018;63(4):447-57. [PMID: 29176636]
11) Rebbeck TR, Friebel TM, Mitra N, et al. Inheritance of deleterious mutations at both BRCA1 and BRCA2 in an international sample of 32,295 women. Breast Cancer Res. 2016;18(1):112. [PMID: 27836010]
12) Susswein LR, Marshall ML, Nusbaum R, et al. Pathogenic and likely pathogenic variant prevalence among the first 10,000 patients referred for next-generation cancer panel testing. Genet Med. 2016;18(8):823-32. [PMID: 26681312]
13) McGuigan A, Whitworth J, Andreou A, et al. Multilocus Inherited Neoplasia Allele Syndrome (MINAS): an update. Eur J Hum Genet. 2022;30(3):265-70. [PMID: 34983940]
14) Megid TBC, Barros-Filho MC, Pisani JP, et al. Double heterozygous pathogenic variants prevalence in a cohort of patients with hereditary breast cancer. Front Oncol. 2022;12:873395. [PMID: 36003761]
15) Momozawa Y, Iwasaki Y, Parsons MT, et al. Germline pathogenic variants of 11 breast cancer genes in 7,051 Japanese patients and 11,241 controls. Nat Commun. 2018;9(1):4083. [PMID: 30287823]
16) Kammula AV, Schäffer AA, Rajagopal PS. Characterization of Oncology Clinical Trials Using Germline Genetic Data. JAMA Netw Open. 2022;5(11):e2242370. [PMID: 36383380]
17) Konstantinopoulos PA, Norquist B, Lacchetti C, et al. Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer:ASCO Guideline. J Clin Oncol. 2020;38(11):1222-45. [PMID: 31986064]
18) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic, Version 3. 2024. (accessed 2024-08-26)
19) Rehm HL, Alaimo JT, Aradhya S, et al. The landscape of reported VUS in multi-gene panel and genomic testing: Time for a change. Genet Med. 2023;25(12):100947. [PMID: 37534744]
20) Ricker C, Culver JO, Lowstuter K, et al. Increased yield of actionable mutations using multi-gene panels to assess hereditary cancer susceptibility in an ethnically diverse clinical cohort. Cancer Genet. 2016;209(4):130-7. [PMID: 26908360]
21) Shirts BH, Casadei S, Jacobson AL, et al. Improving performance of multigene panels for genomic analysis of cancer predisposition. Genet Med. 2016;18(10):974-81. [PMID: 26845104]
22) Idos GE, Kurian AW, Ricker C, et al. Multicenter Prospective Cohort Study of the Diagnostic Yield and Patient Experience of Multiplex Gene Panel Testing For Hereditary Cancer Risk. JCO Precis Oncol. 2019;3:PO.18.00217. [PMID: 34322651]
23) Tsaousis GN, Papadopoulou E, Apessos A, et al. Analysis of hereditary cancer syndromes by using a panel of genes:novel and multiple pathogenic mutations. BMC Cancer 2019;19(1):535. [PMID: 31159747]

24) Agiannitopoulos K, Pepe G, Tsaousis GN, et al. Copy Number Variations(CNVs)Account for 10.8% of Pathogenic Variants in Patients Referred for Hereditary Cancer Testing. Cancer Genomics Proteomics 2023;20(5):448-55. [PMID: 37643779]

25) Bowles KR, Mancini-DiNardo D, Coffee B, et al. Hereditary cancer testing challenges:assembling the analytical pieces to solve the patient clinical puzzle. Future Oncol. 2019;15(1):65-79. [PMID: 30113232]

26) Mancini-DiNardo D, Judkins T, Kidd J, et al. Detection of large rearrangements in a hereditary pan-cancer panel using next-generation sequencing. BMC Med Genomics. 2019;12(1):138. [PMID: 31623605]

BQ4

What should be considered when providing genetic counseling with MGPT?

◎ Statement

Genetic counseling before and after MGPT requires an understanding of the characteristics of MGPT and evidence for each gene covered, in addition to the basic matters of genetic counseling for hereditary cancer syndromes (Chapter 1). Then, the following points should be particularly discussed with patients:

- The possibility that MGPT may detect GPV in genes for which the risk management method and penetration rate are unknown
- The possibility that MGPT may detect unexpected GPV
- High detection rate of VUS, as well as responses to be taken upon its detection
- No insurance coverage (as of March 2025)

◎ Background

The genes analyzed in MGPT include those for which there are no recommended methods of risk management and those for which there is insufficient evidence on the risk of cancer onset. As of August 2024, any type of MGPT performed in Japan is not covered by insurance, and there are differences in the target disease region and number of genes included in the testing. In this context, it is necessary to provide psychosocial support that enables patients to make autonomous decisions regarding which testing to choose, "how much to know or not to know," and "when to undergo the testing," and MGPT requires some cautions that differ from those for SSGT.

◎ Commentary

Individuals who have GPV in cancer susceptibility genes causative of hereditary cancer syndromes need to be provided with appropriate medical management based on their diagnosis. When treating an individual with a hereditary cancer syndrome, medical professionals need to provide support with continued medical management necessary for the individuals and their blood relatives. While the elements of genetic counseling for hereditary cancer syndromes are the same for any type of genetic testing to be considered, unique considerations need to be given when performing MGPT.

1. Pre-testing genetic counseling

1. Evaluation of family history (→See Chapter 5: Methods for describing family tree)

MGPT can be performed without assuming a specific disease, and compared to SSGT, it places less emphasis on pre-testing evaluation of family history to narrow down cancer susceptibility genes in genetic testing. However, when GPV is detected in cancer susceptibility genes for which there is insufficient evidence for medical management, we must carefully interpret the variant and consider clinical responses.

At this time, clinical significance is evaluated by considering the age of the proband at onset, clinical information specific to the detected cancer susceptibility gene (medical history, including non-cancer benign diseases), and family history (e.g., familial clustering), highlighting the importance of pre-testing evaluation of family history.

2. Provision of disease-related information

Because MGPT analyzes multiple cancer susceptibility genes, it is difficult to provide patients with an overview of all diseases prior to performing MGPT, unlike in SSGT. If diseases can be narrowed down based on the client's clinical background, their information should be provided to the client. On the other hand, if no specific disease can be assumed, it is practical to provide an overview of hereditary tumor syndromes and consider medical management based on the results of MGPT.

3. Provision of information on the characteristics of MGPT

It should be noted that there are advantages and cautions for MGPT as it provides a large amount of information, and they should be mentioned to patients when providing preliminary information (Table 2-4).

Table 2-4. Advantages and cautions for MGPT

Advantages	・MGPT is unlikely to overlook GPV since it covers a large number of cancer susceptibility genes. ・To some extent, a negative result can rule out the risks associated with hereditary cancer syndromes at the time of testing
Cautions	・MGPT may detect GPV in genes with a low to moderate risk for which the method of managing medical risks and penetration rate are unknown [3-1)]. ・MGPT may detect unexpected GPV [3-2)]. ・MGPT has a high detection rate of VUS [3-3)].

1) Possibility that MGPT may detect GPV in genes for which the risk management method and penetration rate are unknown

Genes analyzed in MGPT are broadly divided into two categories: (1) genes for which risk management method has been clearly stated based on medical evidence or consensus (e.g., genes for which there have been publications, such as domestic/international clinical practice guidelines) and (2) genes for which risk management method is unclear due to insufficient evidence or consensus (e.g., genes for which no clinical practice guidelines or papers with high levels of evidence are available). Also, MGPT may include genes for which there is insufficient evidence on the degree of risk of tumor development. Patients must be fully informed in advance that the analysis includes genes for which there is insufficient evidence, as described in (2) above. With reference to domestic and international clinical practice guidelines, a system for responding upon detection of GPV needs to be established in one's own facility or collaboration with other facilities. It is desirable to respond to hereditary cancer syndromes with reference to domestic clinical practice guidelines if available. If no domestic treatment guidelines are available for the hereditary cancer

syndrome, we must consider the implementation system at the facility, share information and collaborate with different medical departments, and provide optimal medical care according to the client's individual circumstances, while referring to the items described in Chapters 3 and 4.

2) Possibility that MGPT may detect unexpected GPV

As described in BQ1 and BQ3, patients undergoing MGPT should be informed that the testing may detect GPV in multiple causative genes of hereditary cancer syndromes (MINAS) and that it may detect GPV that is not expected based on an individual's medical or family history. The mutual effects of MINAS on the phenotype (penetration rate, age at onset, and severity), as well as appropriate methods of risk management for individuals with MINAS, are not known since there is little data available. Currently, it is considered appropriate to take recommended measures for each GPV detected. Also, because the transmission of GPV to blood relatives depends on the positional relationship of the loci where each GPV is present, each individual should be explained the predicted probability of GPV before testing.

3) High detection rate of VUS, as well as responses to be taken upon its detection

MGPT has a higher detection rate of VUS than SSGT[1, 2] (→**See BQ3**). When VUS is detected, patients often misinterpret or incorrectly remember testing results. To avoid this, patients should be fully informed during pre-testing genetic counseling that MGPT may detect VUS, and testing results should be given to patients in a written or other physical format.

4. Support for making decisions on the selection of MGPT

MGPT is broadly classified into two types: cancer-specific MGPT (cancer-specific panel) and comprehensive MGPT (comprehensive cancer panel). Cancer-specific MGPT (e.g., the breast cancer panel and the colorectal cancer panel) can be selected when the target organ or hereditary cancer syndrome is assumed. On the other hand, comprehensive MGPT, which examines a large number of genes in a more comprehensive manner, is selected when targets cannot be easily narrowed down. While there are recommended methods of medical management for some genes, both types of MGPT may include genes with a low to moderate risk for which there are no known management methods, and comprehensive MGPT may reveal associations with unexpected hereditary cancer syndromes.

An overseas report showed that, among the patients who were offered MGPT, 4.8% selected a genetic test targeting a smaller number of genes[1]. In a Singapore study, two types of panel testing (breast cancer panel: 7–11 genes including *BRCA1/2, CDH1, PALB2, PTEN, STK11*, and *TP53*; comprehensive MGPT: 19–80 genes) were offered to patients with breast and ovarian cancer, and they received an average of 1.5 genetic counseling sessions before deciding on the testing type[2]. Also, the decision on the type of genetic testing was made at the first genetic counseling session in 57.4% (152/265) of the patients, at the second session in 38.1% (101/265), and at the third session in 4.5% (12/265). The selection of the type of genetic testing was influenced by ethnicity and cancer type, but not family history. Regarding the cancer type, 1/3 of patients with breast cancer chose to undergo breast cancer panel testing, which yielded a result in a shorter time after testing. This suggests that patients' intention regarding the decision on breast cancer treatment plan influences their decision-making regarding which testing to choose. These characteristics of MGPT should be shared with patients in advance, and "how much information to know or not to know" should be clarified. Taking costs into consideration, it is important to confirm patients' thoughts about the

testing, as well as their thoughts and feelings about diseases, including which type of MGPT to select if there are options and whether or not to undergo genetic testing.

Along with the selection of MGPT, a decision on which genetic testing (MGPT, SSGT, or single-site analysis) to choose should be made in consideration of the risk assessment of various hereditary cancer syndromes based on family information and the financial burden of the individual (not only whether or not the testing is covered by insurance but also the cost-effectiveness perceived by the individual). During genetic counseling, testing is selected according to the individual's intention.

As of August 2024, MGPT is not covered by insurance in Japan, and information on GPV obtained from the results of MGPT cannot be used for companion diagnostics. Also, the circumstances of each client need to be taken into account when considering "for what, when, and to what extent" genetic testing should be undertaken, such as prioritization of treatment-related genetic testing and cost burden. Furthermore, for patients in whom SSGT detected no GPV, a system needs to be established to inform them about the possibility that additional useful information may be obtained by undergoing MGPT.

Therefore, during pre-testing genetic counseling, the following points need to be thoroughly discussed with patients after understanding the characteristics of MGPT and the evidence for each gene to be tested (Table 2-5).

If a client chooses not to undergo genetic testing, it is important to provide medical management according to individual risk assessment and to inform them that he/she can continue to receive genetic counseling throughout his/her life.

Table 2-5. Key points of genetic counseling given prior to MGPT

Purpose of testing	Significance of genetic diagnosis and cautions
Contents of the testing	Genes to be tested, testing results to be obtained, limitations of the testing, methods of disclosing testing results, costs, etc.
Medical management methods according to testing results	Risks, medical management methods, etc., for patients and blood relatives (Detailed information can be provided only if diseases can be narrowed down.)
Information shared with blood relatives	Appropriate timing, genetic testing methods for blood relatives, etc.

2. Genetic counseling at the time of disclosing testing results

Upon detection of GPV, a surveillance plan is presented according to clinical practice guidelines, and consultation is coordinated with relevant departments. When GPV is detected in a gene that is not expected from clinical symptoms, the client must be provided with detailed explanations of the disease and support for encouraging appropriate health behavior while confirming the status of acceptance of the

result. Consultation regarding follow-up based on disease guidelines should be given to individuals who have been diagnosed with a hereditary cancer syndrome for which there is accumulated evidence.

Ongoing genetic counseling is needed for patients with GPV or those who are concerned about their genetics, even if they do not have GPV. A study showed that 231 individuals, including those undergoing MGPT, exhibited no psychological changes 6 or 12 months after genetic counseling. On the other hand, psychological changes were analyzed in 249 individuals who underwent MGPT after no GPV was detected by *BRCA1/2* genetic testing, and they exhibited a tendency for cancer-specific distress and increased depressed mood 12 months after the disclosure of testing results, compared to before testing, regardless of the testing result[4]. Therefore, long-term psychological changes vary depending on clients' background, and it is necessary to provide patients with access to genetic counseling not only before testing and upon explanation of the testing result but also throughout their lives.

Social background and family relationships of patients, as well as their concerns, may change over time. Also, recommended risk management may change with the accumulation of evidence. In order to provide optimal medical management, continuous follow-up is necessary for each client who has undergone testing, and a comprehensive support system needs to be established, including a system of collaboration and cooperation with other facilities and psychosocial support, rather than a system focusing only on medical treatment.

***Side note 2-1**

For pediatric cancer patients, SSGT may be preferentially selected depending on the cancer type, but MGPT may be selected if the gene cannot be tested by SSGT. In such cases, pathogenic variants may be detected in genes that are not considered to be associated with their cancer type (e.g., heterozygous variants in *BRCA1* in children diagnosed with Peutz-Jeghers syndrome). In particular, we must consider when to communicate with an individual about his/her pathogenic variant that needs to be responded to in adulthood or later. Although it also depends on the age of the individual, it is important to discuss with the parents or guardians the circumstances under which it can be appropriately communicated to the individual before adulthood. Additionally, genetic counseling should be provided with an awareness that the information is also useful for the health management of the parents.

■ References

1) Hall MJ, Patrick-Miller LJ, Egleston BL, et al. Use and Patient-Reported Outcomes of Clinical Multigene Panel Testing for Cancer Susceptibility in the Multicenter Communication of Genetic Test Results by Telephone Study. JCO Precis Oncol. 2018;2:PO.18.00199. [PMID: 31819920]
2) Courtney E, Li ST, Shaw T, et al. Predictors of next-generation sequencing panel selection using a shared decision-making approach. NPJ Genom Med. 2018;3:11. [PMID: 29736259]
3) Gould D, Walker R, Makari-Judson G, et al. Experiences of individuals with a variant of uncertain

significance on genetic testing for hereditary cancer risks:a mixed method systematic review. J Community Genet 2022;13(4):371-9. [PMID: 35819584]

4) Kilbride MK, Egleston BL, Hall MJ, et al. Longitudinal follow-up after telephone disclosure in the randomized COGENT study. Genet Med. 2020;22(8):1401-6. [PMID: 32376981]

BQ5

How do we interpret the pathogenicity of variants?

◎ Statement

All variants detected by MGPT must be assessed for their pathogenicity, for which the evaluation should be based on the 2015 ACMG/AMP guidelines. Where available, gene-specific criteria released by the U.S. Clinical Genome Resource (ClinGen) should be applied to enhance the accuracy of interpretation[#1]. Variants are evaluated through the following procedure: After confirming the notation and location of the variant, information on the variant is collected from databases and literature, and the pathogenicity of the variant is interpreted and evaluated based on criteria.

Variants with a ClinVar review status[#2] of 3 stars or higher for the relevant phenotype (RCV) may be evaluated using their ClinVar classification after confirming their association with the disease. When using population databases[#3], such as gnomAD[#3] and ToMMo[#3], careful attention should be paid to the presence of variants characteristic of the Japanese population.

DNA information alone may be insufficient for the interpretation of pathogenicity of some variants, and the use of RNA-based evidence, such as the effects on RNA splicing, should also be considered (**see Column**).

◎ Background

The American College of Medical Genetics and Genomics (ACMG) previously issued recommendations on the interpretation of variant pathogenicity[1)], which have been used in various settings. However, advances in the technology of base sequence analysis have led to an increase in the number of reports on genes associated with hereditary diseases, dramatically increasing the number of variants detected. With this background, the ACMG jointly established a working group with the Association for Molecular Pathology (AMP) and the College of American Pathologists (CAP) and developed the 2015 ACMG/AMP guidelines with updated contents covering definitions of terms and detailed guidance for variant classification[2)]. However, the 2015 ACMG/AMP guidelines broadly cover variants in the causative genes of Mendelian genetic diseases, and the evaluation criteria based on the characteristics of each disease are largely left to the discretion of the evaluator.

Also, variants registered in ClinVar are evaluated differently depending on the evaluator, and different interpretations are often made for the same variant[3)]. Furthermore, the Sequence Variant Interpretation (SVI) Working Group[#4] of ClinGen issued a variety of recommendations on the use of the 2015 ACMG/AMP guidelines[4)], increasing the complexity of the situation. Variants in some genes can be evaluated according to their characteristics and phenotypes using gene-specific criteria for variant evaluation developed by the Variant Curation Expert Panels (VCEP)[#5 5-8)]. On the other hand, information required for the evaluation of variants has been segmented, and we may not be able to obtain sufficient information necessary for evaluation in some cases. Genetic variants for which no specific method of evaluation is available are often evaluated with varying accuracy, which can lead to differences in the interpretation of their pathogenicity among facilities.

The present BQ describes a consistent process from the evaluation and interpretation of variants detected by MGPT at testing companies to reporting to requesting physicians, which is important for accurate and reproducible interpretation of variant pathogenicity.

◎ Commentary

1. Evaluation of variant pathogenicity based on the 2015 ACMG/AMP guidelines

The 2015 ACMG/AMP guidelines classify variant pathogenicity into five categories: "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" (Figure 2-2). Variant pathogenicity is interpreted through the evaluation of combined evidence for the criteria met by each variant[#6]. Based on the type of evidence, the criteria are divided into "pathogenic" and "benign," each of which is classified into "very strong," "strong," "moderate," or "weak" according to the strength of the evidence. For the use of the criteria and the strength of evidence to be applied, various recommendations have been issued by the SVI after the release of the 2015 ACMG/AMP guidelines, and it should be noted that usage method of some criteria have been changed and that the use of some criteria is no longer recommended, including the "Pathogenicity interpretation using reliable databases (PP5/BP6)."

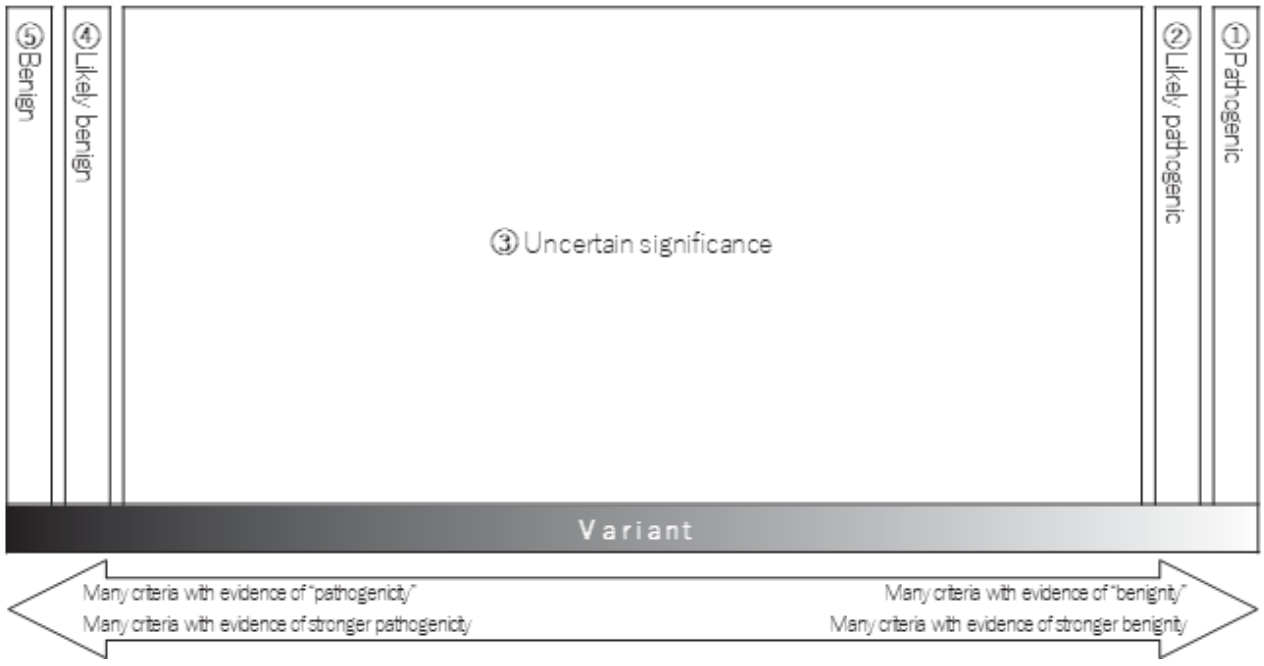


Figure 2-2. Five categories [(1) to (5)] of variant pathogenicity according to the ACMG/AMP guidelines

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#1: Clinical Genome Resource (ClinGen)

ClinGen is an institution funded by the U.S. National Institutes of Health (NIH). It is working to build a database that can be used for precision medicine and research by clarifying the clinical significance of genes and their variants.

#2: ClinVar review status

The information registered in ClinVar is managed with three accession numbers: an accession number for each registered variant (SCV), an accession number for each phenotype based on the aggregated information of registered variants (RCV), and an accession number for the entire aggregated variants (VCV). The review status for each accession number, which is expressed as the number of stars ranging from 0 to 4, indicates the level of evaluation of the registered interpretation, with a higher number of stars indicating a higher reliability of the registered information.

#3: Population database

Population databases contain information on allele and genotype frequencies of variants in the general population.

The ToMMo database contains genomic information of the general Japanese population (excluding third-degree relatives and abnormalities of sex chromosome karyotypes) analyzed by the Tohoku Medical Megabank Organization.

The gnomAD database, provided by the U.S. Broad Institute, contains genomic information of various genetic ancestry (race) groups compiled by an international consortium, although data on the Japanese population are scarce. The database does not include pediatric disease cohorts, but some datasets, such as those of biobanks, may include individuals having serious diseases with a low frequency. In gnomAD, datasets of populations that were not identified as having cancer in cancer studies can also be used as a reference.

In any of the databases, we should fully consider the possibility that a small number of causative variants of hereditary tumor syndromes may be included.

#4: Sequence Variant Interpretation (SVI) Working Group

The SVI Working Group provides support to improve uniformity and consistency among expert panel groups that are refining gene- or disease-specific ACMG guidelines. It consists of representatives from each group.

#5: Variant Curation Expert Panels (VCEP)

VCEP is a working group organized within ClinGen, consisting of experts who evaluate the evidence for classifying the presence or absence of pathogenicity in genetic variants for specific diseases.

#6: Criteria (PVS, BS, PM, BP, PP, etc.)

The criteria refer to the evaluation criteria used in the ACMG guidelines to interpret the pathogenicity of variants. They are divided into 'criteria that serve as the basis for pathogenicity' and 'criteria that serve as the basis for benignity,' and they are classified according to the level of evidence and type of criteria. Interpretation of variant pathogenicity is determined by the combination of criteria applied.

2. Limitations and cautions for the interpretation of variant pathogenicity using the 2015 ACMG/AMP guidelines

The very strong evidence in the 2015 ACMG/AMP guidelines is "null variants in genes where loss of function is the disease-causing mechanism." This restricts the use of the criteria in evaluating variants in genes where a disease is caused by other mechanisms (e.g., *POLE*, in which abnormalities in certain functional domains are associated with diseases, and *RET* in multiple endocrine neoplasia type 2, in which gain of function is associated with disease onset), affecting the accuracy of interpretation[9]. Also,

interpretation of non-truncating variants, such as missense variants, is often difficult in case reports of concordance between the variant and phenotype within a family (co-segregation) or the same variant, as well as in cases with no functional analysis data. Furthermore, because some criteria are judged differently depending on the evaluator, ClinVar often presents different interpretations for the same variant[3, 10].

Splicing abnormalities, structural variants, and variants in untranslated regions may not be fully evaluated using only one DNA-based method[11, 12]. It is important to understand that it may be difficult or impossible to detect some variants depending on the NGS platform used and that the information obtained may differ depending on the reference sequence used. Some websites, such as VarSome[#7] (https://varsome.com/) and Franklin[#8] (https://franklin.genoox.com/clinical-db/home), can evaluate variants based on the 2015 ACMG/AMP guidelines, but it should be noted that each of these websites has its own criteria.

3. Cautions to be taken when using gene-specific criteria

As of August 2024, some genes associated with hereditary tumor syndromes have gene-specific criteria created by VCEP (Table 2-6)[5-8].

A study re-evaluated previously reported variants using new criteria and published its findings, recommending that gene-specific criteria be used for those genes[13]. Since many cases require clinical information specific to each disease, it enables precise evaluation, but a lack of sufficient information can make the interpretation challenging, as described below. In addition, criteria that use information from the analysis of tumors, such as mutational signature[#9] and microsatellite instability (MSI), are also being considered[14].

Table 2-6. Genes for which the criteria for gene-specific pathogenicity interpretation have been established by the VCEP

Genes	Handling in this guide
APC [p. 142], *ATM* [p. 143], *BRCA1/2* [p. 149, 150], *CDH1* [p. 152], *DICER1* [p. 156], MMR genes [p. 166, 167, 169, 175], *PALB2* [p. 174], *PTEN* [p. 178], *RAD51C* [p. 180], *TP53* [p. 193]	Chapter 4, "Causative genes of hereditary tumor syndromes and their management" (The numbers in brackets indicate the page number in this guide.)
RUNX1	Not covered in this guide

#7: VarSome

VarSome is a community-driven knowledge database. When a variant is entered, VarSome automatically collects information based on the criteria of the ACMG guidelines, applies the criteria in a unique approach, and displays interpretation results. Additionally, VarSome shows information assigned by community members.

#8: Franklin

The Franklin database is similar to Varsome, but it collects slightly different information.

#9: Mutational Signature

Mutational signature refers to a pattern of mutations that have occurred in the genome of cancer cells. The pattern of mutations is known to vary depending on the cause. The patterns are published on the website of the Catalogue of Somatic Mutations in Cancer (COSMIC), and single-base substitutions alone have more than 50 types.

4. Responses to be taken when a variant is determined to be VUS based on pathogenicity interpretation

If evidence for the criteria met by a variant does not meet the standard for determining the presence or absence of pathological significance, the variant is interpreted as VUS (**Figure 2-2**). Missense variants, short in-frame insertion/deletion variants, and deep intronic variants are often interpreted as VUS[13]. However, these variants may be interpreted as pathogenic (or benign) through experimental validation, such as RNA-based analysis of splicing abnormalities[12]. Also, when using gene-specific criteria, a variant may be interpreted as VUS based on insufficient information to meet the criteria or the unavailability of some information due to changes in the criteria. Furthermore, some variants that are frequently registered only in the Japanese population may not be evaluated because the criteria do not include information on the allele frequency for Asian races, including the Japanese. When a variant is determined to be VUS based on pathogenicity interpretation, consideration may be given to whether the interpretation has been made based on sufficient information, whether additional validation is needed, and how information that is not included in the criteria should be evaluated.

5. Databases and tools used for variant evaluation

Currently, the 2015 ACMG/AMP guidelines do not recommend that the pathogenicity interpretation of variants listed in databases be used directly for evaluation (PP5/BP6)[4]. However, as mentioned above, pathogenicity interpretation may not be fully evaluated due to a lack of sufficient information or the limitation of allele frequency information of the Japanese population. Therefore, pathogenicity interpretation of variants may be used directly if it has been registered in ClinVar and reviewed by VCEP curators[#10] (with a review status of 3 stars or higher for RCV). Additionally, databases that aggregate variant frequencies in the general population worldwide or in Japan, as well as gene-specific databases, have been used, and there are databases that aggregate information on the association between variants and diseases, mainly in the Japanese population.

In addition, tools for predicting the impact of base sequence changes on splicing and gene function, as well as tools for scoring specific phenotypes, are available. When using databases or tools, it is necessary to understand their versions and characteristics. Since some criteria use data from functional evaluation[15] or case-control[16] studies of variants, it is important to keep up to date with the latest information.

6. Responses to be taken when the pathogenicity interpretation of a variant is difficult

The interpretation of variant pathogenicity is confirmed by combining a variety of information, including common information such as position and alteration, information from databases, and phenotypes. Therefore, as mentioned above, there may be cases where confirmation of pathogenicity interpretation is difficult, such as when there is insufficient information according to the criteria or when an interpretation is supported by the information that is not included in the criteria. In addition, depending on the information on the variant or the evaluation method, responses to VUS may need to be taken assuming an interpretation biased in one direction or the other rather than assuming completely uncertain significance. Also, GPV specific to a certain ethnic group may be reported as VUS[17]. Thus, if pathogenicity interpretation is difficult, the final interpretation and clinical responses should desirably be discussed by multiple experts (→ See **Column: "Consultation system for variant interpretation"**).

However, because the outcome of discussions may differ from facility to facility, it is important to establish a base site for discussions and share information in real time. Also, in order to facilitate smooth discussions among experts, the use of data analyzed by Japanese researchers and appropriate guidance on the actionability for VUS[18-20] are expected to be necessary. In fact, the Association for Clinical Genomic Science (ACGS) in the United Kingdom recommends its criteria based on the 2015 ACMG/AMP guidelines and classifies VUS according to the pathogenic potential[21]. Furthermore, for gene-specific criteria, the Cancer Variant Interpretation Group UK has issued recommendations specific to the United Kingdom[22]. Further discussions are needed on the interpretation criteria using information other than the existing criteria, as well as on the interpretation criteria unique to Japan.

7. Need for the re-evaluation of variants

Even after it has been established, interpretation of variant pathogenicity may change based on clinical findings, updated information in databases, use of gene-specific criteria, and re-evaluation using new literature data. In the re-evaluation of variants, a downgrade from VUS to the 'benign' or 'likely benign' category is most common, accounting for approximately 70% of cases, while an upgrade to the 'pathogenic' or 'likely pathogenic' category is few, accounting for only approximately 7% of cases[23]. Although very rare, a change may be made to the interpretation of variants that have been assigned a pathogenicity rating other than VUS, and it is important to establish a system for regular re-evaluation[23].

8. Responses for low-penetrance variants and risk alleles

Recommendations are being released by the ClinGen Low-Penetrance/Risk Allele Working Group[#11], but they are currently under review[24].

9. Evaluation process and database registration of the results of pathogenicity interpretation

Sharing variant information using databases is important for improving the accuracy of interpretation of variant pathogenicity[18]. It is recommended that the results of interpretation, together with evidence, be promptly registered in public databases, such as ClinVar and MGeND[25], especially for variants whose pathogenicity interpretation is difficult[26].

10. Process of evaluation and interpretation to be included in reports

Some variants of the same gene may present different phenotypes (phenotypic heterogeneity), such as Hirschsprung disease and multiple endocrine neoplasia type 2 caused by *RET* variants, and evaluations using gene-specific criteria can vary greatly depending on clinical findings. Given these issues, reports must describe the evaluation/interpretation made, evidence used, and disease examined using disease classifications, such as OMIM®#12 and Mondo#13 [26]. Interpretation should be promptly re-evaluated if new information that could affect the interpretation is obtained.

#10: Curator

Variants are curated by biocurators of ClinGen who have taken the designated training course. They belong to each VCEP, and a ClinVar review status of 3 stars is given to variants that have been evaluated and interpreted by the curators in the VCEP.

#11: ClinGen Low-Penetrance/Risk Allele Working Group

The ClinGen Low-Penetrance/Risk Allele Working Group, organized within ClinGen, is working to develop definitions of the terms for low-penetrance variants and risk alleles, as well as a framework for their evaluation and classification.

#12: OMIM®

Online Mendelian Inheritance in Man® (OMIM®) is a comprehensive catalog of human genes and genetic phenotypes, and it is updated almost daily. OMIM® contains information on all known Mendelian genetic diseases, as well as over 16,000 genes.

#13: Mondo

The Mondo Disease Ontology (Mondo) integrates multiple disease ontologies.

11. Facilities interpreting variant pathogenicity

In principle, variants should be evaluated and re-evaluated by testing companies using information in public databases to the extent possible, and the results of pathogenicity interpretation should be reported to medical institutions. However, due to the complexity of gene-specific criteria and the need for experimental validation, it is necessary to discuss which institution should be responsible for the process leading up to the final pathogenicity interpretation, including the measures to be taken when

pathogenicity interpretation is difficult and the system for the re-evaluation of variants, as mentioned above.

Column: Consultation system for variant interpretation

In overseas countries where MGPT is widely performed, each facility or testing company implements MGPT-based genomic medicine through the establishment of a consultation system for variant interpretation in genetic medical treatment, although it varies by country or region.

A consultation system for variant interpretation is expected to involve re-examination of variant evaluation process by experts, as well as decisions on appropriate pathogenicity interpretation and future responses, in different situations, such as when there is doubt about the pathogenicity interpretation made by the testing company, when there is a discrepancy between the pathogenicity interpretation and the phenotype, and when future medical management needs to be discussed. If germline genetic information serves as companion diagnostics for a therapeutic agent, its indication should be discussed in collaboration with an expert panel for CGP testing. If necessary, it may be examined not only within a facility but also across multiple facilities or on a national scale. Ideally, such a consultation system should include experts in genetic medicine, clinical testing, data analysis, molecular biology, and related diseases. The outcome of discussions made under the consultation system should be promptly shared in public databases in order to prevent inconsistencies in responding to variants among facilities.

■ References

1) Richards CS, Bale S, Bellissimo DB, et al. ACMG recommendations for standards for interpretation and reporting of sequence variations:Revisions 2007. Genet Med. 2008;10(4):294-300. [PMID: 18414213]

2) Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants:a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-24. [PMID: 25741868]

3) Harrison SM, Dolinsky JS, Knight Johnson AE, et al. Clinical laboratories collaborate to resolve differences in variant interpretations submitted to ClinVar. Genet Med. 2017;19(10):1096-104. [PMID: 28301460]

4) ClinGen. SVI General Recommendations for Using ACMG/AMP Criteria. https://clinicalgenome.org/working-groups/sequence-variant-interpretation/(accessed 2024- 08-26)

5) Lee K, Krempely K, Roberts ME, et al. Specifications of the ACMG/AMP variant curation guidelines for the analysis of germline *CDH1* sequence variants. Hum Mutat. 2018;39(11):1553-68. [PMID:

30311375]
6) Mester JL, Ghosh R, Pesaran T, et al. Gene-specific criteria for *PTEN* variant curation:ecommendations from the ClinGen PTEN Expert Panel. Hum Mutat. 2018;39(11):1581-92. [PMID: 30311380]
7) Fortuno C, Lee K, Olivier M, et al. Specifications of the ACMG/AMP variant interpretation guidelines for germline *TP53* variants. Hum Mutat. 2021;42(3):223-36. [PMID: 33300245]
8) Spier I, Yin X, Richardson M, et al. Gene-specific ACMG/AMP classification criteria for germline APC variants:Recommendations from the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Variant Curation Expert Panel. Genet Med. 2024;26(2):100992. [PMID: 37800450]
9) Mur P, Viana-Errasti J, García-Mulero S, et al. Recommendations for the classification of germline variants in the exonuclease domain of POLE and POLD1. Genome Med. 2023;15(1):85. PMID: 37848928]
10) Amendola LM, Jarvik GP, Leo MC, et al. Performance of ACMG-AMP Variant-Interpretation Guidelines among Nine Laboratories in the Clinical Sequencing Exploratory Research Consortium. Am J Hum Genet. 2016;98(6):1067-76. [PMID: 27181684]
11) Thibodeau ML, O'Neill K, Dixon K, et al. Improved structural variant interpretation for hereditary cancer susceptibility using long-read sequencing. Genet Med. 2020;22(11):1892-7. [PMID: 32624572]
12) Truty R, Ouyang K, Rojahn S, et al. Spectrum of splicing variants in disease genes and the ability of RNA analysis to reduce uncertainty in clinical interpretation. Am J Hum Genet. 2021;108(4): 696-708. [PMID: 33743207]
13) Lucci-Cordisco E, Amenta S, Panfili A, et al. Variants of uncertain significance (VUS) in cancer predisposing genes: What are we learning from multigene panels? Eur J Med Genet. 2022;65(1):104400. [PMID: 34813939]
14) Walsh MF, Ritter DI, Kesserwan C, et al. Integrating somatic variant data and biomarkers for germline variant classification in cancer predisposition genes. Hum Mutat. 2018;39(11):1542-52. [PMID: 30311369]
15) Rayner E, Tiersma Y, Fortuno C, et al. Predictive functional assay-based classification of PMS2 variants in Lynch syndrome. Hum Mutat. 2022;43(9):1249-58. [PMID: 35451539]
16) Momozawa Y, Iwasaki Y, Parsons MT, et al. Germline pathogenic variants of 11 breast cancer genes in 7,051 Japanese patients and 11,241 controls. Nat Commun. 2018;9(1):4083. [PMID: 30287823]
17) Yamazawa K, Sugano K, Tanakaya K, et al. The pathogenic role of the *BRCA2* c.7847C>T(p.Ser2616Phe)variant in breast and ovarian cancer predisposition. Cancer Sci. 2023;114(7):2993-3002. [PMID: 37067535]
18) Mighton C, Shickh S, Uleryk E, et al. Clinical and psychological outcomes of receiving a variant of

uncertain significance from multigene panel testing or genomic sequencing: a systematic review and meta-analysis. Genet Med. 2021;23(1):22-33. [PMID: 32921787]

19) Chang EY, Solomon I, Culver JO, et al. Clinical and laboratory genetic counselor attitudes on the reporting of variants of uncertain significance for multigene cancer panels. J Genet Couns. 2023;32(3):706-16. [PMID: 36747331]

20) Burke W, Parens E, Chung WK, et al. The Challenge of Genetic Variants of Uncertain Clinical Significance: A Narrative Review. Ann Intern Med 2022;175(7):994-1000. [PMID: 35436152]

21) Science TAfCG. ACGS Best Practice Guidelines for Variant Classification in Rare Disease 2024 v1.2. https://www.acgs.uk.com/quality/best-practice-guidelines/(accessed 2024-08-26)

22) Research TIoC. CanVIG-UK Gene Specific Recommendations. https://www.cangene-canvaruk.org/gene-specific-recommendations(accessed 2024-08-26)

23) Makhnoon S, Levin B, Ensinger M, et al. A multicenter study of clinical impact of variant of uncertain significance reclassification in breast, ovarian and colorectal cancer susceptibility genes. Cancer Med. 2023;12(3):2875-84. [PMID: 36426404]

24) Schmidt RJ, Steeves M, Bayrak-Toydemir P, et al. Recommendations for risk allele evidence curation, classification, and reporting from the ClinGen Low Penetrance/Risk Allele Working Group. Genet Med. 2024;26(3):101036. [PMID: 38054408]

25) Kamada M, Nakatsui M, Kojima R, et al. MGeND: an integrated database for Japanese clinical and genomic information. Hum Genome Var. 2019;6:53. [PMID: 31839973]

26) Rehder C, Bean LJH, Bick D, et al. Next-generation sequencing for constitutional variants in the clinical laboratory, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(8):1399-415. [PMID: 33927380]

BQ6

What is the difference between MGPT and comprehensive genome profiling test using tumor tissue?

◎ Statement

Tumor tissue-based genetic testing is aimed at obtaining information useful for treatment selection based on the genomic profile of tumor tissue, and unlike MGPT, it is not intended to diagnose hereditary cancer syndromes. Comprehensive cancer genome profiling (CGP) testing may detect GPV as a germline finding in the analysis of T/N pair, as well as PGPV in the analysis of tumor tissue only. Thus, it is necessary to provide appropriate genetic medical care by conducting adequate genetic counseling in accordance with the intention regarding the disclosure of germline findings. For PGPV, separate genetic testing (mainly single-site analysis) is needed to confirm the diagnosis of germline or somatic origin. It should be noted that CGP cannot rule out hereditary cancer syndromes, as it may not detect pathological structural abnormalities, such as structural variation (SV), even in the genes included in the report (false negative).

Genetic counseling, including the presentation of the option to select MGPT, should be provided to individuals who exhibit no germline findings in CGP despite having a phenotype suggestive of a hereditary cancer syndrome.

◎ Background

With the growing use of CGP in health insurance medical care, there has been a dramatic increase in the number of cases where the estimation of GPV or PGPV as a germline finding has led to the diagnosis of a hereditary tumor syndrome. The genes specified in the ACMG Recommendations can be used as references for determining which genes should be disclosed for germline findings in CGP[1]. In Japan, the materials of the “Guidelines for Communication Processes in Genomic Medicine” are widely used based on the ACMG Recommendations (FY 2017–2019 AMED Genomic Drug Discovery Infrastructure Promotion Research Project “Research to Promote the Practical Application of Genome Information Research to Medical Care,” FY2020–2022 Ministry of Health, Labour and Welfare Sciences Research Grant “Extraction of Ethical and Social Issues and Improvement of Social Environment Toward Realization of a Society in which the Public Can Receive Genome Medicine with Peace of Mind,” and FY2023: Liaison Conference of Core Hospitals for Cancer Genome Medicine, SFWG)[2-4]. As of August 2024, five types of CGP are covered by insurance in Japan, and it should be noted that the responses to germline findings differ depending on the type of specimen used.

Different types of testing are available: testing using tumor tissue only (T-only), testing using circulating tumor DNA (ctDNA) from blood specimens (liquid biopsy), and testing that simultaneously examines tumor tissue and non-tumor specimen (mainly blood specimen) (T/N pair)[2]. When PGPV is found in the gene to be disclosed in CGP, a test to confirm the variant (single-site test) is required. This also applies to cases where PGPV is identified in the causative gene of hereditary tumor syndromes by the companion diagnostics using tumor tissue only (e.g., MyChoice® Diagnostic System). Because CGP is not designed for comprehensively diagnosing the causative genes of hereditary tumor syndromes, it is not used as a

substitute for genetic diagnostic testing. In addition, it has been reported that some pathogenic variants in hereditary tumor syndrome-related genes detected in normal tissues are likely derived from clonal hematopoiesis of indeterminate potential (CHIP) or somatic mosaic state[5]. Thus, even in CGP using T/N pair specimens, it is desirable to understand the type of genes disclosed as germline findings. Also, upon detection of a variant, clinical information, including medical and family history, and the detection status of the variant in T/N pair specimens should be reviewed, followed by confirmatory testing, as appropriate. Furthermore, because CGP analyzes only short DNA sequences using a next-generation sequencer, it often does not detect (or report) SVs, such as deletions of exon units, given the accuracy of the testing. Therefore, based on the limitations of CGP testing, necessary measures should be taken, including reviewing phenotypes suggestive of hereditary cancer syndromes prior to the testing.

◎ Commentary

1. Detection rate of GPV, as well as responses to be taken upon its detection

The C-CAT database in T/N pair testing is a useful reference for the detection rate of GPV in CGP in Japan. Of the 886 cases in the OncoGuide™ NCC Oncopanel System, 36 (4.1%) were determined to have GPV by the expert panel[6]. Also, it should be noted that until its version update in February 2021, germline variants were reported only for 13 (sequencing report) out of 114 genes to be analyzed (currently, information on germline variants can be obtained for all 124 genes to be analyzed). The ESMO Precision Medicine Working Group reported that 3,627 GPVs were detected (corresponding to 8.0%) in 45,472 patients with solid cancer who had undergone MSK-IMPACT (468 genes analyzed) as T/N-pair CGP[7]. A study that included WES and RNA sequencing reported that GPV was detected in 15.8% of cases when the analysis included GPV in genes causative of ARD diseases (such as *MUTYH*)[8]. Considering MGPT as a standard, GPV is estimated to be present in approximately 10% of cancer patients (even when limited to those with a pattern of AD inheritance). It should also be noted that some of the variants detected in normal specimens may be derived from CHIP associated with aging or treatment course. Upon detection of GPV, it is important to provide genetic counseling to the individual and blood relatives as soon as possible, according to the intention for disclosing germline findings.

2. Detection rate of PGPV, as well as responses to be taken upon its detection

The detection rate of PGPV in CGP (T-only or liquid biopsy) in Japan was reported to be 9.6% (229 out of 2,396 individuals) in the FoundationOne® CDx and FoundationOne® Liquid CDx Cancer Genome Profile. GPV was found in 15 (30.6%) of 49 individuals who had undergone genetic confirmatory testing for diagnosis[6]. Although the detection rate of GPV was calculated to be only 3.0%, it should be noted that genes with a high positivity rate for pathogenic variants in tumor tissue and a low germline conversion rate*, such as *TP53*, are usually not recommended for disclosure as PGPV[2, 7]. An overseas study of over 125,000 cases reported that PGPV was detected in 9.7% of cases[9]. Single-site analysis is usually selected for genetic confirmatory testing of PGPV. The genes analyzed in single-site analysis differ depending on the testing company, and the companies need to be able to perform single-site analysis of multiple genes, including the genetic testing on blood relatives conducted after MGPT. It is also important to take into consideration the process leading up to the single-site analysis of the individual and responses to be taken

for blood relatives, as well as to keep in mind not to delay the timing of CGP testing.

***: Germline conversion rate**
The proportion of germline variants among variants detected in tumor tissue[10)]

3. Companion diagnostics using tumor tissue

The MyChoice® Diagnostic System (which evaluates *BRCA1/2* pathogenic variants and HRD in tumor tissue) is widely used as companion diagnostics for T-only testing to select drugs in initial treatment, mainly for advanced ovarian cancer. A study in Japan showed that the BRACAnalysis® Diagnostic System detected GPV in 42 of the 55 patients positive for *BRCA1/2* pathogenic variants in tumor tissue (germline conversion rate: 76.3%)[10)]. Additionally, 2 (1.3%) of the 150 patients who had been diagnosed as negative for *BRCA1/2* pathogenic variants (or VUS) by the MyChoice® Diagnostic System were diagnosed as positive by the BRACAnalysis® Diagnostic System[10)]. Because the MyChoice® Diagnostic System also determines the presence or absence of HRD using a genomic instability score, MGPT is also considered for individuals negative for *BRCA1/2* pathogenic variants and positive for HRD in tumor tissue, with HRD-related genes in mind. Immunohistochemistry testing for MMR-related genes *MLH1, MSH2, PMS2,* and *MSH6* has also come to be used as companion diagnostics, but it should be noted that a negative result from the testing cannot completely rule out Lynch syndrome.

4. Patients' intention

In Japan, it was shown that only approximately 2% of individuals who underwent CGP did not express an intention to disclose germline findings[6)], suggesting that there may be an expectation that germline findings lead directly to treatment. On the other hand, because cancer patients who have completed standard treatment suffer from significant physical pain and psychological conflicts, they may have difficulty in expressing their intentions, and genetic counseling may be delayed due to the priority given to treatment[11)]. In CGP, consideration needs to be given to the fact that many individuals undergo the testing with different processes and motivations from those undergoing conventional genetic counseling or testing (based on family or medical history). Since many germline findings are detected not only in related cancers (on-tumor) but also in non-related cancers (off-tumor)[7)], we need to take sufficient time to provide an explanation on germline findings before CGP testing and to support patients in making decisions.

5. Patients' satisfaction

Patients' satisfaction with CGP testing varies greatly depending on whether or not it has led to treatment[12)]. On the other hand, knowing germline findings does not necessarily lead to lower patient satisfaction. In a nationwide actual condition survey in Japan, 64.6% of patients expressed satisfaction with CGP testing with a score of 7 or higher on an 11-point scale from 0 to 10, and the most common

reason for high satisfaction was “I was able to think about the risk of cancer in my family” at 45% (multiple answers were allowed)[13]. Disclosure of germline findings in CGP is expected to lead to an improvement in patient satisfaction.

6. Cost

Regarding PGPV, genetic testing for the diagnosis of hereditary cancer syndromes, as well as genetic counseling for blood relatives, is not covered by insurance, which increases the economic burden on patients and their families. Reduction in the financial burden in all aspects of CGP-based genetic medicine is desired.

■ References

1) Miller DT, Lee K, Abul-Husn NS, et al. ACMG SF v3.2 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023;25(8):100866.[PMID: 37347242].

(2) Health and Labor Sciences Research Funded Research Project on Ethical and Legal Social Issues, "Extraction of Ethical and Social Issues and Improvement of Social Environment for Realization of a Society in which People can Receive Genomic Medicine with Peace of Mind" (Principal Investigator: Shinji Kosugi, Kyoto University). Guidelines for communication processes in genomic medicine Part 2: Specific policies for germline comprehensive genetic testing using next-generation sequencers [Revision 2] 20210908. (Reference 2024-08-26).

(3) Health and Labor Sciences Research Funded Research Project on Ethical and Legal Social Issues "Extraction of Ethical and Social Issues and Improvement of Social Environment for Realization of a Society in which People can Receive Genomic Medicine with Peace of Mind" (Principal Investigator: Shinji Kosugi, Kyoto University). Guidelines for Communication Process in Genomic Medicine Part 1: Focusing on Cancer Genome Testing [Revised 3rd Edition] 20210908 (. Reference 2024-08-26)

(4) Liaison Conference of Core Hospitals for Cancer Genome Medicine, Working Group on Secondary Findings (SFWG). Cancer Gene Panel Test Secondary Findings Patient Disclosure Recommendation List (Ver4.2_20231003). 2023.
https://www.ncc.go.jp/jp/c_cat/jitsumushya/030/Potentially_Actionable_SF_Gene_List_Ver4.2_20231003.pdf (reference 2024-08-26)

Current status and issues related to secondary findings in the first public insurance covered tumor genomic J Hum Genet. 2022;67(10):557-63.

6) Satake T, Kondo S, Tanabe N, et al. Pathogenic Germline Variants in BRCA1/2 and p53 Identified by Real-world Comprehensive Cancer Genome Profiling Cancer Res Commun. 2023;3(11):2302-11. [PMID: 37916805].

7) Kuzbari Z, Bandlamudi C, Loveday C, et al. Germline-focused analysis of tumour-detected variants in

49,264 cancer patients: ESMO Precision Medicine Working Group recommendations. Ann Oncol. 2023;34(3):215-27. [PMID: 36529447].

8) Cobain EF, Wu YM, Vats P, et al. Assessment of the Clinical Benefit of Integrative Genomic Profiling in Advanced Solid Tumors. JAMA Oncol. 2021;7(4):525- 33. [PMID: 33630025].

9) Tung N, Dougherty KC, Gatof ES, et al. Potential pathogenic germline variant reporting from tumor comprehensive genomic profiling complements NPJ Precis Oncol. 2023;7(1):76. [PMID: 37568048].

10) Oda K, Aoki D, Tsuda H, et al. Japanese nationwide observational multicenter study of tumor BRCA1/2 variant testing in advanced ovarian cancer. Cancer Sci. 2023;114(1):271-80: 36254756]

11) Nagai A, Ri I, Muto K. Attitudes toward genomic tumor profiling tests in Japan: patients, family members, and the public. J Hum Genet. 2019; 64(5): 481- 5.[PMID: 30631119].

12) Meiser B, Butow P, Davies G, et al. Psychological predictors of advanced cancer patients' preferences for return of results from Am J Med Genet A. 2022; 188(3):725-34. PMID: 34755933

13) Kage H, Akiyama N, Chang H, et al. Patient survey on cancer genomic medicine in Japan under the national health insurance system. Cancer Sci. 2024;115(3):954-62. [PMID: 38273803].

BQ7

What responses should be taken when variants are found in genes for which there is insufficient evidence of association with the risk of disease onset?

◎ Statement

MGPT and comprehensive genome analyses, such as whole genome analysis, may detect variants in genes for which there is insufficient evidence of association with the risk of disease (cancer) onset. If variants are detected in such genes among those tested (analyzed), their information may be listed in the testing report. Such findings generally do not provide information that can lead to subsequent medical management, including surveillance and preemptive medical treatment. However, evidence accumulated in the future may reveal their association with the risk of disease onset that could be subject to medical management. Provision of information on health management measures to variant carriers of the relevant genes may lead to the need for proposing surveillance and preemptive medical treatment. Therefore, it is necessary to regularly review the evidence for such genes, to organize and respond to the evidence at the time of disclosing results, and to inform patients that additional reports may be made in the future.

◎ Background

Chapters 3 and 4 summarize information on genes and diseases for which relatively sufficient evidence has accumulated. However, MGPT and comprehensive genome analyses, such as whole genome analysis, provided by various testing companies cover genes that are not listed in Chapters 3 and 4 (as of August 2024). Even if variants that are thought to affect the function of these genes are detected, there is often insufficient evidence for their association with the risk of disease onset. Also, the evaluation of an association with the risk of disease onset may change in the future.

◎ Commentary

1. Range of genes for which there is insufficient evidence

Evidence for genes associated with the risk of cancer onset is summarized by organ in Chapter 3 and by gene in Chapter 4. A relatively large number of clinical and basic studies have been conducted on the cancer onset risks of the genes listed in Chapters 3 and 4, and it has been determined that they can be explained and addressed with a certain degree of certainty at present. However, testing companies may offer MGPT that analyzes genes not listed in Chapters 3 and 4. These include genes whose risk of disease onset has been statistically shown by large-scale analyses, such as genome-wide association studies (GWAS) (i.e., genes associated with a slight increase in the risk of disease onset), as well as genes whose association with disease onset has been shown by case reports. Even if variants that are thought to affect the function of these genes are detected, there is insufficient evidence for the clinical usefulness of the

genes in medical management, and the genes are also referred to as a “gene of uncertain significance (GUS). When the testing report provided by the testing company lists the results of such genes, it is necessary to carefully read the explanation provided, and the person requesting the testing should review the latest evidence on the disease onset risk of the genes at that time.

2. Responses to be taken for genes for which there is insufficient evidence

If a testing report indicates that a variant has been detected in a gene that may be GUS, then the detected variant should be evaluated again based on the procedure for interpreting variant pathogenicity described in BQ5. If the result predicts that it may affect the function of the gene, the next step is to review the evidence for an association of the gene with an increased risk of disease onset. If there is sufficient evidence for an increased risk of disease onset, the client should be informed of the risk, and a response plan should be discussed. On the other hand, if the reported gene is judged to be GUS, provision of explanations and responses should be considered during the genetic counseling provided at the time of disclosing the testing result in accordance with the cautions to be taken upon detection of VUS, as described in BQ4. It has been reported that when patients are presented with an ambiguous result, they take measures to reduce the ambiguity by collecting additional information, participating in clinical studies, or recommending genetic testing to blood relatives[1]. On the other hand, even if there is insufficient evidence at the time of receiving the result from the testing company, additional evidence is expected to accumulate in the future, which may lead to the consideration of medical management according to the risk of disease onset. Therefore, patients should be informed about the possibility that additional reports may be made in the future. Based on these, MGPT should desirably be performed by individuals with sufficient knowledge of clinical genetics who are familiar with the characteristics and limitations of the testing, and appropriate genetic counseling should be provided before and after the testing, as described in BQ3. Also, in order to respond to patients’ anxiety about ambiguous results and additional reports, the medical institution requesting the testing should have a system for providing information and genetic counseling continuously.

3. Changes in genes covered by MGPT due to the accumulation of evidence

The genes covered by MGPT change as evidence accumulates; in the future, some genes, mainly those that could be GUS, may be found to be associated with hereditary cancer syndromes, while others may be found to have no association with hereditary cancer syndromes. Chapter 4 summarizes the association between genes and hereditary cancer syndromes, but it should be noted that it is based only on current evidence.

■ Reference

1) Scherr CL, Ramesh S, Getachew-Smith H, et al. How patients deal with an ambiguous medical test: decision-making after genetic testing. Patient Educ Couns. 2021;104(5):953-9: 33214013]

BQ8

What should be considered when managing the accuracy of genetic testing for hereditary cancer syndromes?

◎ Statement

When performing genetic testing, it is necessary to thoroughly consider the significance of the testing individually to determine its necessity, as well as to use the testing for making clinical judgments while always being aware of how its accuracy is ensured. For this, some basic principles can be used as references, including the ACCE model proposed by the U.S. Centers for Disease Control and Prevention (CDC) **(Commentary 1)**, as well as the "Basic Principles for Ensuring the Quality and Accuracy of Cancer Gene Panel Testing" and the "Basic Principles for Quality Assurance of Genetic Testing, Particularly Regarding External Accuracy Evaluation" presented by the Japanese Promotion Council for Laboratory Testing (**Commentary 2**). In Japan, a system to ensure the accuracy of comprehensive gene-related testing is currently being established. However, it is important to keep in mind that all processes, from the collection and storage of specimens to measurements and result interpretation, lead to the provision of correct testing results (**Commentary 3**).

◎ Background

The Act for Partial Revision of the Medical Care Act (Act No. 57) came into effect in December 2018[1, 2] in response to further dramatic progress in the practical application of genome medicine, including cancer genome medicine, and the growing need to ensure the accuracy of gene-related testing necessary for that purpose. In this revised Medical Care Act, the classification of "gene-related chromosomal testing" was newly established independently within specimen testing, and standards and regulations for its implementation were established (**Commentary 2**).

On the other hand, the system for conducting testing while ensuring accuracy has not been sufficiently developed in some disease areas where genetic testing is essential for diagnosis, and the actual situation has not kept up with the revision of the law.

Based on this current situation, the MHLW research project of "Research on Clarification of Standards for Ensuring Accuracy of Gene-related Chromosomal Testing" (22IA1007)[3] summarized various issues in current gene-related chromosomal testing and proposed methods for conducting external surveys on accuracy management. Furthermore, the research project of the A Research Team for a Quality Control System for Laboratory Tests in the Field of Intractable Diseases (H30-Intractable Diseases-018)[4]

investigated the actual status of genetic testing in the field of intractable diseases in Japan and formulated "Guidelines for Genetic Testing in the Treatment of Intractable Diseases" in March 2021[5]. Traditionally, genetic testing for rare intractable diseases has been conducted in university laboratories and similar facilities as an extension of research due to the lack of testing facilities capable of providing such testing. However, the guidelines showed that medical care and research must be separated, given the need to ensure the quality and accuracy of genetic testing used in medical care.

◎ Commentary

1. ACCE model

The U.S. Centers for Disease Control and Prevention (CDC) has proposed the ACCE model as a basic principle to be considered for providing reliable genetic testing[6]. ACCE is an acronym for the following items:

- Analytic validity: whether the testing has been established (e.g., the same results can be obtained no matter how many times the testing is performed or at which facility the testing is performed)
- Clinical validity: whether the relationship between testing results and diseases has been established
- Clinical utility: whether there is any treatment for patients who have been diagnosed with a disease through the testing
- ELSI (ethical, legal, and social issues): whether ethical, legal, and social issues have been considered

The need to take these into consideration when conducting genetic testing has been shown. In principle, these include the following: to perform the testing using an established method for genes (and their variants) that have clear pathogenicity for diseases with a clear disease concept, as well as to consider whether or not to include blood relatives in the testing in consideration of factors such as the form of inheritance and penetration rate. When performing genetic testing on patients, we must consider each item of ACCE and provide appropriate testing to patients who need it.

2. Assurance of the accuracy of genetic testing (related to the Medical Care Act)

The 2018 amendment to the Medical Care Act stipulated the items to be observed when conducting gene-related chromosomal testing, as shown in Table 2-7 (excerpted)[1, 2].

Table 2-7. Items to be observed when performing gene-related chromosomal testing

Item	Content
Assignment of person in charge	To assign a person responsible for ensuring the system performs gene-related chromosomal testing
Preparation of standard procedures, etc.	To prepare standard operating manuals for the maintenance of testing equipment and measurement procedures, as well as work diaries and various ledgers
Implementation of	To carry out necessary calibration of equipment and reagents in daily

internal accuracy management	testing and measurements, as well as to periodically record and review variations using control specimens, etc.
Participation in external surveys on accuracy management	To make efforts to undergo external surveys on accuracy management conducted by various organizations

Currently, measurements conducted in university laboratories (except for those recognized as registered health laboratories and clinical laboratories in hospitals) cannot be positioned as medical care with ensured quality[3]. Measures should be taken, such as conducting testing in facilities that comply with the Medical Care Act, with reference to the guidance set by the Namba Group of the Ministry of Health, Labour and Welfare[4], as shown in the "Background" section. When disclosing the results of genetic analysis conducted in laboratories or similar settings, patients should be informed that they are the results of the testing conducted as research and are to be treated as reference information[5, 7].

3. Accuracy management of gene-related testing organized by the implementation process

The Japanese Promotion Council for Laboratory Testing has presented principles for accuracy management in gene-related testing based on the proposals of "Basic Principles for Ensuring the Quality and Accuracy of Cancer Gene Panel Testing"[8] and "Basic Principles for Quality Assurance of Genetic Testing, Particularly Regarding External Accuracy Evaluation"[9]. Based on these, testing is generally divided into "pre-analysis process," "analysis process," and "post-analysis process," showing that the validity of testing should be confirmed for each process and that quality control should be conducted.

When performing genetic testing, including MGPT, at one's own facility, the ACMG technical standards are used as a reference[10]. The present BQ does not necessarily assume that the entire process of MGPT is carried out at one's own facility, and it is intended mainly for the testing outsourced to registered health laboratories and other facilities. However, the "pre-analysis process" and "post-analysis process" play an important role in obtaining accurate testing results, even at medical institutions that request testing.

1. Pre-analysis process

In the "pre-analysis process," the test recipients and target genes are first determined with reference to the disease phenotype, family history, and other factors. For example, if testing with a sensitivity and specificity of 99% is performed on a gene with a GPV frequency of 0.2%, then the accuracy rate of detecting GPV is calculated to be approximately 17%. On the other hand, if we limit a population by family history and other factors and perform the same testing on the population with a GPV frequency of 10%, then the positive predictive rate would be increased to approximately 92%. This is also important when considering target genes for MGPT, and the false-positive rate increases with an increase in the number of genes to be searched for at one time.

Patients who have previously undergone hematopoietic stem cell transplantation may have a mixture of donor-derived and recipient-derived blood cells, and in such patients, the accuracy of genetic testing cannot be guaranteed, which may make it difficult to determine testing results using the conventional measurement methods with blood cell-derived nucleic acids. Furthermore, to ensure the consistent extraction of high-quality nucleic acids, procedures must be established for the type of blood collection tube used, methods of storage and transportation of specimens after collection (temperature and time), and other processes. If formalin-fixed, paraffin-embedded tissue specimens are used for testing for any reason, they should be prepared in accordance with the Regulations for Handling Histopathological Specimens for Genomic Medicine[11], in principle.

2. Analysis process

The analysis process of MGPT mainly refers to the process of extracting nucleic acids from specimens, preparing a library for sequencing, and determining the base sequence of the region to be analyzed. This process is expected to be performed by an external measurement institution as outsourced testing, but medical institutions need to continually verify that outsourcing companies meet the technical requirements for the testing.

3. Post-analysis process

In the "post-analysis process," it is important to review whether the testing has been carried out properly by referring to various quality indicators (e.g., the total number of reads, coverage uniformity, and average depth are reviewed for analyses conducted using next-generation sequencers) described in the report provided by the analysis institution. Also, it is necessary to accurately annotate the variant information provided and to prepare a consistent report on the presence or absence of an association with diseases. These processes require the ability to refer to various disease-related databases and interpret relevant literature information.

However, an external system for managing the accuracy of gene-related testing has not been sufficiently established in Japan, which has been an issue. In the United States, all laboratories are accredited under the Clinical Laboratory Improvement Amendments (CLIA), and the scope of accreditation is indicated according to the content of the testing to be performed. In addition, the quality and implementation system of testing are evaluated by the College of American Pathologists (CAP) and other federally approved accreditation bodies. Currently, testing for medical care that uses reagents and measurement systems developed at one's own facility (laboratory developed test: LDT) is conducted under such a system. On the other hand, Japan has no established external survey program for managing the quality of comprehensive gene-related testing, although the international standard ISO 15189 is widely used as an accreditation system for clinical laboratories, and the quality management is carried out mainly in the form of participating in the programs conducted by overseas institutions, such as CAP surveillance. LDT itself has not been clearly defined, and the system for implementing LDT as insurance medical care has only just begun to be considered. Therefore, a clear framework to ensure the accuracy of genetic testing has

not yet been established, and relevant stakeholders need to come together to establish a system promptly.

■ References

(1) Act for Partial Revision of the Medical Care Act, etc. (Act No. 57 of 2009) . June 14, 2009 .
https://www.shugiin.go.jp/internet/itdb_housei.nsf/html/housei/19320170614057.htm

(2) Ministry of Health, Labour and Welfare. Enforcement of the Ministerial Ordinance Concerning the Establishment of Ministerial Ordinances Related to the Ministry of Health, Labour and Welfare in Relation to the Partial Enforcement of the Act for Partial Revision of the Medical Care Act, etc. [Act on Clinical Laboratory Technicians, etc.] (Medical Policy Bulletin No. 0810, No. 1). August 10, 2008.
https://www.mhlw.go.jp/web/t_doc?dataId=00tc3586&dataType=1&pageNo=1 (reference 2024-08-26)

(3) Health and Labor Sciences Research Grant, Research Project for the Promotion of Regional Medical Infrastructure Development, "Research on Clarification of Standards for Ensuring Accuracy of 'Gene-related and Chromosome Tests'" (Principal Investigator: Miyaji, H.). Research on Clarification of Standards for Ensuring Accuracy of "Gene-related and Chromosome Tests" Research Report. 2023.
https://mhlw-grants.niph.go.jp/project/164772 (reference 2024-08-26)

(4) Grant-in-Aid for Scientific Research on Diseases and Disorders, Intractable Disease Policy Research, "Research contributing to the development of an accuracy management system for specimen testing in the area of intractable diseases" (Principal investigator: Eiji Namba). Research to contribute to the development of an accuracy management system for specimen testing in the field of intractable diseases Research report.2021.
https://mhlw-grants.niph.go.jp/project/147124 (reference 2024-08-26)

(5) Health and Labour Sciences Research Grant, Research on Intractable Diseases Policy Research Project, Research Group for the Improvement of the Accuracy Management System for Specimen Testing in the Field of Intractable Diseases. Guidelines for genetic testing in the treatment of intractable diseases, March 31, 2021.
http://www.kentaikensa.jp/files/35773.pdf (reference 2024-08-26)

(6) Centers for disease control and prevention (CDC). ACCE Model Process for Evaluating Genetic Tests.
https://archive.cdc.gov/#/details?q=ACCE&start=0&rows=10&url=https://www.cdc.gov/genomics/gtesting/acce/index.htm

(7) Japan Medical Association. Guidelines for Genetic Testing and Diagnosis in Medical Care (Revised March 2022). 2022.
https://jams.med.or.jp/guideline/genetics-diagnosis_2022.pdf (reference 2024-08-26)

(8) Japan Council for the Promotion of Clinical Laboratories. Basic approach to ensuring the quality and accuracy of cancer gene panel tests (Version 2.0). 31 May 2019.
https://www.jamt.or.jp/data/asset/docs/20190531_ver2.0.pdf (reference 2024-08-26)

(9) Subcommittee on Gene-related Testing, Japan Association for the Advancement of Clinical Laboratories. Basic approach to quality assurance of gene-related tests, particularly with regard to external accuracy assessment. 24 March 2023.
https://www.jpclt.org/news/detail/20230327092844/ (reference 2024-08-26)
10) Rehder C, Bean LJH, Bick D, et al. Next-generation sequencing for constitutional variants in the clinical laboratory, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(8):1399-415.[PMID: 33927380].
(11) Japanese Society of Pathology. Regulations for the Handling of Histopathology Specimens for Genomic Medicine. 2018.
https://pathology.or.jp/genome_med/pdf/textbook.pdf

BQ9

What precautions should be taken when handling genetic information?

◎ Statement

The results of MGPT serve as information that can be used not only by the individual but also by current and future blood relatives. By sharing the information with medical professionals of various specialties, it can be reflected in high-quality team medical care. On the other hand, MGPT may yield unexpected results or detect a large number of VUSs. Given these characteristics, attention should be paid to the following points regarding the handling of genetic information obtained by MGPT:

- All information reported in genetic testing results should be recorded in medical records.
- To ensure information sharing and avoidance of disadvantages to test recipients, all personnel in medical facilities are required to participate in educational and awareness-raising activities on the characteristics of genetic information and its handling (personnel safety management measures).
- MGPT may detect pathogenic variants in genes that are not associated with the originally assumed disease or genes that are not expected, and it may detect VUS at a high frequency. Medical institutions need to have clear policies on the handling of these aspects.
- When sharing testing results with other medical institutions, the medical institution providing the results should individually discuss the content and scope of the results to be shared.
- There are likely few opportunities that genetic information of a patient needs to be shared with parties outside of medical institutions. However, if such a situation arises, a decision should be made after carefully considering the characteristics of the genetic information, the significance of providing the information, and the benefits and disadvantages to the test recipient.

◎ Background

The “handling” discussed in the present BQ refers to the handling not only in medical records but also in other situations.

1. Handling medical records

Despite the provisions of the Medical Practitioners Act, there remains confusion and hesitation regarding the inclusion of genetic testing results in medical records. This is due to the "genetic exceptionalism," an idea that originated in the late 20th century[1]. In the 1990s, the research aspect of genetic testing was emphasized, and in societies, some test recipients suffered disadvantages due to the inappropriate handling of genetic information. In light of these, it was widely thought at the time that genetic information should be given a special status different from that of other medical information. This idea was adopted by the "International Declaration on Human Genetic Data" released by UNESCO in 2003 and the "Guidelines for Genetic Testing" (abolished in 2022) released by 10 genetic societies in Japan in the same year.

However, the position of genetic testing has gradually shifted from research to medical information used in general practice, and as some tests began to be covered by insurance, the previous way of thinking became a hindrance to the use of genetic information in medical practice. Also, due to advances in genetic medicine and increasing awareness of genetic medicine among not only medical professionals but also the general public, it became necessary to establish guidance appropriate to the situation at the time. With this background, the "Guidelines for Genetic Testing and Diagnoses in Medical Care" were newly formulated by the Japanese Association of Medical Sciences in 2011. The guidelines clearly stated that the results of genetic testing of disease-affected individuals should be recorded in medical records in the same manner as other medical information. The guidelines were revised in 2022[2], further stating that records of genetic counseling, in addition to genetic information, should be included in medical records, in principle. Genetic information can be widely utilized today, and it should be treated as medical information useful for diagnosis and treatment, without being excessively concerned about the disadvantages to test recipients caused by leakage or misuse of genetic information when providing medical care. Also, we need to be strongly aware of the risks to blood relatives that may arise from not being able to share information appropriately.

2. Handling outside of medical records

A survey of the general public conducted by Muto et al. of the University of Tokyo showed that approximately 3% of respondents had experienced discrimination or disadvantages related to genetic information[3, 4].

◎ Commentary

1. Recording of testing results in medical records

Article 24 of the Medical Practitioners Act stipulates that "when a physician has provided medical treatment, he/she must record the matters related to the medical treatment in medical records without delay." Genetic testing is a matter related to medical treatment, and it is needless to say that the Article applies to genetic testing. Furthermore, since the "Benefits for Medical Record Management System" in

the current insurance medical care requires central management of all medical records, it cannot be denied that additional fees charged while separately managing some medical records may be regarded as fraudulent charges.

Currently, many electronic medical records used in Japan store testing results in a specific folder so that the treatment course can be followed up over time. However, genetic testing results, which remain unchanged throughout a person's life, may become lost in a large amount of information, making their search difficult. In order to ensure that genetic information can be shared appropriately among medical professionals and used smoothly in medical care, it is necessary to devise ways to describe and record genetic testing information in an easy-to-search format. Since the interpretation and clinical utility of genetic information may change in the future, information on unexpected genetic variants and VUS should also be included when recording the results of MGPT.

In genetic medicine, genetic testing results of blood relatives may be provided along with a referral letter or other information, and they may be recorded in electronic medical records. Therefore, measures to prevent unintentional switching of testing results between the individual and blood relatives are also essential from the perspective of risk management.

2. "Genetic exceptionalism"

The concept of so-called "genetic exceptionalism" originated from a proposal made by bioethicist George Annas in 1993. In addition to the characteristics that genetic information remains unchanged throughout life (invariance) and may be shared among blood relatives with a certain probability (covalency), it can also be "harmful" when it is socially misused, such as in eugenics, and it can cause psychological harm to society. Thus, Annas argued that genetic information is "special information that requires special protection and regulation." He also considered genetic information in the DNA bank as "future diaries." Even then, this idea was opposed by arguments such as the following: (1) genetic information is merely a part of sensitive medical information that may infringe on the interests of the individual, (2) genetic information is practically indistinguishable from other medical information, and (3) there is no morally important difference between genetic information and other clinical testing information.

With subsequent discussions and generalization of genetic information in general practice, it has become generally recognized that the disadvantages of treating genetic information as an exception cannot be ignored and that genetic information is not exceptional, although it requires consideration based on its characteristics.

3. "Guidelines for Genetic Testing and Diagnoses in Medical Care" by the Japanese Association of Medical Sciences

The first edition, released in 2011, stated that attending physicians are responsible for explaining genetic testing to disease-affected patients and obtaining their consent. It also noted that, in principle, the results

of genetic testing in patients who have already developed the disease must be recorded in the medical records, just like other test results. However, in the case of diagnosing disease-free carriers, pre-onset conditions, or conducting prenatal diagnosis, it stated that genetic counseling is required before testing, but did not mention whether the results should be recorded in the medical records.

In the 2022 revised edition, the content has been updated to reflect advances in genetic medicine. It now states that, in principle, both the results of genetic testing and the content of genetic counseling should be documented in the medical records. At the same time, to ensure adequate protection of individuals undergoing testing, the revision emphasizes the importance of providing healthcare professionals with basic knowledge of genetic medicine and sufficient education and training in the proper handling of personal genetic information. This is to ensure that enhanced documentation does not compromise the privacy and protection of those being tested.

4. Act on the Comprehensive and Planned Promotion of Measures to Ensure that the Public Can Receive High-quality and Appropriate Genomic Medicine With Peace of Mind

In Japan, the Act was enacted in June 2023 as a result of long-term efforts made by those involved in the promotion of genomic medicine and laws prohibiting discrimination and disadvantages based on genetic information. The Act set out the following basic principles: (1) to realize the world's highest standard of genome medicine, (2) to provide appropriate consideration for bioethics at each stage of research development and provision, and (3) to prevent unfair discrimination based on genome information.

■ References

1) Yoshio Nukaga and Kiichiro Tsutani. Trends in the Issue of "Genetic Exceptionalism." Journal of the Japan Medical Association. 2006; 134(12): 2385-90.
2) Japanese Association of Medical Sciences. Guidelines for Genetic Testing and Diagnoses in Medical Care (Revised March 2022). 2022. https://jams.med.or.jp/guideline/genetics-diagnosis_2022.pdf (reference 2024-08-26)
3) Ministry of Health, Labour and Welfare Sciences Research Grant, Field of Administrative Policy Research, Special Research of the Ministry of Health, Labour and Welfare Sciences "Survey Study on the Actual Condition of the Use of Personal Genetic Information and Genome Literacy in Society" (Principal Investigator: Kaori Muto). Research Report of the Survey Study on the Actual Condition of the Use of Personal Genetic Information and Genome Literacy in Society. 2017. https://mhlw-grants.niph.go.jp/project/25825 (reference 2024-08-26)
4) Uchiyama M, Nagai A, Muto K. Survey on the perception of germline genome editing among the general public in Japan. J Hum Genet. 2018;63(6):745-8. [PMID: 29545588]

1) Nukaga, Yoshiro and K. Tsutani. Trends in the "genetic exceptionalism" issue. Journal of the Japan Medical Association. 2006; 134(12): 2385-90.

(2) Japan Medical Association. Guidelines for Genetic Testing and Diagnosis in Medical Care (Revised March 2022). 2022.
https://jams.med.or.jp/guideline/genetics-diagnosis_2022.pdf (reference 2024-08-26)

(3) Grant-in-Aid for Scientific Research on Health, Labour and Welfare, Field of Administrative Policy Research, Health Labour Science Special Research "Investigation Study on the Actual Condition of Personal Genetic Information Utilization and Genome Literacy in Society" (Principal Investigator: Kaori Muto). Research Report of the Survey on the Actual Condition of Personal Genetic Information Use and Genome Literacy in Society.2017.
https://mhlw-grants.niph.go.jp/project/25825 (reference 2024-08-26)

4) Uchiyama M, Nagai A, Muto K. Survey on the perception of germline genome editing among the general public in Japan. J Hum Genet. 2018; 63(6): 745-8.[PMID : 29545588]

FQ1

How are whole-exome sequencing (WES) and whole-genome sequencing (WGS) different from MGPT?

◎ Statement

Compared to MGPT, comprehensive genome analyses, such as WES and WGS, cover a broader range of genomic regions and are expected to increase the detection rate of GPVs associated with the diagnosis of hereditary cancer syndromes. Additionally, whole genome analyses allow for the simultaneous evaluation of hereditary predispositions to disease onset, including assessments such as PRS based on disease-associated variants identified through GWAS and other methods.

However, the testing accuracy, including analytical validity, clinical validity, and clinical utility, of comprehensive genome analyses has not been as thoroughly validated as that of MGPT. These analyses may identify hereditary diseases not detectable by MGPT, generate a high number of VUSs, and reveal SVs. Further consideration is required regarding methods for genomic data analysis, variant interpretation, and the disclosure and management of results.

◎ Background

Advances in genome analysis technology have enabled the acquisition of human WGS data at relatively low cost and in a short time. Currently, Genomics England (UK)[1], the German Cancer Consortium (Germany)[2], the Hartwig Medical Foundation (Netherlands)[3], and other organizations are investigating the clinical implementation of WGS in cancer. In Japan, based on the “2022 Whole Genome Analysis, etc. Action Plan”[4], studies are being conducted to establish a system for obtaining comprehensive genomic data, including WGS and RNA-seq, in the fields of cancer and intractable diseases, and to return analysis results to research participants.

Comprehensive genome analyses, such as WES and WGS, may be covered by insurance in the future, in addition to CGP, which is currently being implemented in medical practice. However, the analytical validity, clinical validity, and clinical utility of comprehensive genome analyses have not been sufficiently reviewed and evaluated for their future medical implementation. Since comprehensive genome analyses may yield findings that lead to the diagnosis of hereditary diseases, even outside the tumor area, it is necessary to establish a system for considering the explanation of consent before testing, confirmation of

intention to disclose results, assessment and management of risks for each disease after disclosure, data management, and future notifications to patients.

◎ Commentary

1. Current state of medical implementation of comprehensive genome analyses (progress in each country)

With the spread of NGS, cancer studies using comprehensive genome analyses have been conducted at various research institutions. A representative example is the WGS study by the International Cancer Genome Consortium (ICGC), which was established in 2008 to promote cancer research and treatment by conducting comprehensive cancer genome analyses under international collaboration and sharing and publishing the findings among researchers. Through participation in the project, researchers in Japan have been working on the analysis of some cancer types, and the findings were published as Pan-Cancer Analysis of Whole Genomes in 2020[5]. In addition, the Hartwig Medical Foundation in the Netherlands and other organizations are building a system for clinically narrowing down analysis target genes to develop gene panel testing while accumulating the results of whole genome analysis, and they are working to implement it in medical practice.

2. Characteristics, utility, and targets of comprehensive genome analyses

Currently, insurance-covered CGP only targets fewer than 1,000 genes for analysis, and MGPT for hereditary tumor syndromes usually targets fewer than 100 genes for analysis. On the other hand, WES evaluates variants in the coding regions of all genes, and WGS evaluates variants not only in coding regions but also in non-coding regions. However, it is difficult to predict the effects of variants detected in non-coding regions on gene function, and information on transcriptional products (mRNA) can also be important in predicting their effects on gene function. Also, interpretation of variants is expected to advance with whole-genome transcriptome sequencing (WGTS), in which whole-transcriptome sequencing (WTS) is carried out in parallel (**Table 2-8**)[6].

Additionally, the predictability of disease onset risk by polygenic risk score (PRS) has recently been studied based on the results of GWAS[7]. Diseases with a high PRS have been reported to show a risk ratio comparable to that of hereditary tumor syndromes. PRS can also be calculated in WGS. With the accumulation of evidence in the future, WGS is expected to enable risk assessment based on PRS, as well as risk stratification based on modifying factors that coexist with GPV.

Although such comprehensive genome analyses increase the number of genomic regions to be analyzed and the amount of genetic information to be obtained, we believe that at present they should be conducted only as research studies with limited subjects. If we achieve the establishment of infrastructure for comprehensive genome analyses and subsequent data management and demonstrate their validity and usefulness in the future, the establishment of their provision system after sufficient consideration of

patient-public involvement (PPI) and ethical, legal, and social issues (ELSI) may further expand the number of individuals eligible for comprehensive genome analyses.

Table 2-8. Characteristics of comprehensive genome analyses

	MGPT	WES	WGS	WGTS
Analysis target range	Up to several hundred genes (up to approximately 2 M bp)	All genes (45M bp or more)	Whole genome (3G bp)	Whole genome (3G bp)
SNVs/indels	Target region	Exon region	Entire genome region	Entire genome region
Copy number change	-/Limited†	Exon region	Entire genome region*	Entire genome region*
Structural change	-/Limited†	Limited	Entire genome region	Entire genome region
Fusion gene	-/Limited†	Limited	Entire genome region	Entire genome region
Gene expression	-	-	-	+
Change in transcriptional products	-	-	-	+
Analysis cost	+	++	+++	++++
Read depth‡	+++	++	+	+

†: It depends on the design of the target region and the analysis pipeline, ‡: Read depth per cost.
*: Some regions are difficult to evaluate when the reading depth is shallow.

3. Issues regarding analytical validity

Comprehensive genome analyses have unique issues regarding analytical validity. First, because they sequence a wider range of genomic regions, the read depth per cost is less than that of MGPT. For this reason, there may be genomic regions where sufficient accuracy cannot be ensured as the read depth.

In addition, there are many repeat sequences in the genome, mainly in non-coding regions. Also, if there are complex structural abnormalities, it is difficult to completely reproduce the actual structural abnormalities from the analysis results. The analytical validity of comprehensive genome analyses needs to be confirmed through the combined use of multiple genome analysis methods with different principles.

4. Issues regarding clinical validity

Comprehensive genome analyses often identify a large number of variants with uncertain clinical significance. Compared to MGPT, these analyses also include genes associated with lower penetrance and lower disease risk, but clear evidence or guidelines regarding the clinical actionability of such findings remain limited. Furthermore, due to the potential for unexpected results or findings with insufficient supporting evidence, it is essential to provide genetic counseling prior to testing and to establish a response system capable of addressing all types of genetic outcomes.

■ References

1) Turnbull C. Introducing whole-genome sequencing into routine cancer care: the Genomics England 100 000 Genomes Project. ann Oncol. 2018; 29(4): 784- 7.[PMID: 29462260].

2) Horak P, Heining C, Kreutzfeldt S, et al. Comprehensive Genomic and Transcriptomic Analysis for Guiding Therapeutic Decisions in Patients with Rare Cancer Discov 2021;11(11):2780-95. [PMID: 34112699].

3) Samsom KG, Bosch LJW, Schipper LJ, et al. Study protocol: Whole genome sequencing Implementation in standard Diagnostics for Every cancer patient (WIDE). BMC Med Genomics. 2020; 13(1): 169.

(4) Ministry of Health, Labour and Welfare. Whole Genome Analysis Action Plan 2022, September 30, 2022. https://www.mhlw.go.jp/content/10808000/001071539.pdf (reference 2024-08-26)

(5) ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium. Pan-cancer analysis of whole genomes. Nature. 2020;578(7793):82-93.[PMID: 32025007].

6) Cuppen E, Elemento O, Rosenquist R, et al. Implementation of Whole-Genome and Transcriptome Sequencing Into Clinical Cancer Care. JCO Precis Oncol. 2022;6:e2200245.[PMID: 36480778].

7) Torkamani A, Wineinger NE, Topol EJ. the personal and clinical utility of polygenic risk scores. Nat Rev Genet. 2018;19(9):581-90.[PMID: 29789686].

CHAPTER 3. Organ-specific management of hereditary cancer syndromes

Overview of Chapter 3

In Chapter 3, we focus on genes associated with cancer and tumor susceptibility in various organs and describe the medical management, including methods of risk reduction and surveillance, to be provided upon detection of a germline pathogenic variant (GPV), assuming its implementation by clinicians when such variants are detected in the germ line. The genes listed for each organ include those causing the representative hereditary cancer syndromes shown in Table 1-1 in Chapter 1, as well as those covered in Chapter 4. Additionally, Chapter 3 discusses genes that are considered important for the medical management of each organ despite not being included in Chapter 4. At the beginning of each section, we list genes associated with cancer and tumor susceptibility in the specific organ, followed by an overview, surveillance methods (including starting age and intervals), chemoprevention, surgical treatment (including risk-reducing surgery), and drug therapy. If there was no available evidence for a particular item, that item was omitted. The medical management presented in this chapter is a summary of national and international guidelines published up to September 2024; for details, please refer to the original and most recent guidelines.

1. Brain and nervous system

Major hereditary cancer syndromes associated with hereditary brain and nervous system tumors (as well as their causative genes) include neurofibromatosis types 1 and 2 (*NF1*, *NF2*), von Hippel–Lindau disease (*VHL*), tuberous sclerosis (*TSC1*, *TSC2*), Li-Fraumeni syndrome (*TP53*), Cowden syndrome/*PTEN* hamartoma tumor syndrome (*PTEN*), Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*), familial adenomatous polyposis (familial polyposis coli) (*APC*), hereditary pheochromocytoma and paraganglioma syndrome (*SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *MAX*, *TMEM127*), hereditary retinoblastoma (*RB1*), multiple endocrine neoplasia type 1 (*MEN1*), hereditary breast and ovarian cancer (*BRCA1*, *BRCA2*), Nijmegen breakage syndrome (*NBN*), and individuals who carry a germline pathogenic variant (GPV) in *BAP1*, *PALB2*, or *CDKN2A*.

1. Overview

According to the latest WHO classification (WHO Classification of Brain Tumors, 5th Edition (2021)), there are more than 100 subtypes of brain and nervous system tumors. Therefore, a number of tumor subtypes exist even in hereditary cancer syndromes, where brain and nervous system tumors have been reported to occur frequently. Also, a single disease or causative gene does not necessarily lead to the development of only one tumor subtype, and rather, it may cause the development of multiple tumor subtypes. Additionally, it has been reported that brain and nervous system tumors have varying penetration rates depending on the disease or causative gene. Therefore, the method, starting age, and intervals of surveillance, as well as treatment methods, differ slightly depending on the disease and causative gene.

2. Surveillance methods

In patients with hereditary cancer syndromes, surveillance of the brain and nervous system is mainly performed with head and spinal MRI (at intervals of 1–2 (3) years). Contrast-enhanced MRI is employed in many cases since the use of a contrast agent often increases the probability of identifying small tumors. In patients with Li-Fraumeni syndrome, however, if initial contrast-enhanced MRI detects no tumor, subsequent contrast-enhanced MRI is considered unnecessary unless an abnormality is found, given the accumulation of gadolinium[1]. Furthermore, MRI examination is not recommended for all patients with neurofibromatosis type 1 (NF1) since they have a lower incidence rate of brain tumors than those with other hereditary cancer syndromes. Thus, periodic follow-up is recommended for these patients, and MRI examination should be performed upon the appearance of suspicious symptoms[2]. Although many hereditary cancer syndromes with a high incidence of brain and nervous system tumors

have become known, their frequency and course often remain unclear, and surveillance methods have not yet been established for many of the diseases. See **Chapter 4** for gene-specific responses.

3. Starting (and ending) age of surveillance

The starting age, and in some cases the ending age, of surveillance depends on the hereditary cancer syndrome. It is recommended that surveillance be started at the age of 10 to 12 years for patients with neurofibromatosis type 2 (NF2)[3], at the age of 11 years for patients with von Hippel–Lindau (VHL) disease[4], and promptly after diagnosis for patients with Li-Fraumeni syndrome[1]. For patients with tuberous sclerosis, MRI examination is recommended at the time of diagnosis regardless of age, and surveillance may be terminated if there is no new onset of subependymal giant cell astrocytoma (SEGA) by the age of 25 years[5]. Also, surveillance for patients with VHL disease may be terminated at the age of 65 years if no specific lesions are present[4].

4. Surveillance intervals

In patients with hereditary cancer syndromes, MRI surveillance of the brain and nerves is generally performed at intervals of 1–2 (3) years, but the appropriate surveillance interval is determined depending on the presence or absence of lesions and their growth tendency.

5. Surgical treatment

In patients with hereditary cancer syndromes, indications for surgical treatment of brain and nervous system tumors vary depending on the tumor type and disease. For example, if the tumor has a histological type with poor prognosis (e.g., medulloblastoma and glioblastoma), its resection is considered at the time of diagnosis. However, many cases of benign tumors with favorable prognosis (e.g., hemangioblastoma in patients with VHL disease) are followed up since they are often asymptomatic, even at the time of diagnosis (for detailed indications, see “Guide to the Clinical Treatment of von Hippel–Lindau Disease”[6]). Resection of neurilemoma in NF2 patients should be considered based on the presence or absence of associated clinical symptoms (e.g., hearing loss) or growth tendency (for details, see “Treatment Guidelines for Neurofibromatosis Type 2”[7]).

6. Radiotherapy

In patients with hereditary cancer syndromes, the usefulness of radiotherapy for brain and nervous system tumors varies depending on the disease. Radiotherapy, such as Gamma Knife, may be useful for hemangioblastoma in patients with VHL disease, as well as neurilemoma in patients with NF2[6, 7]. In contrast, the usefulness of radiotherapy for SEGA in patients with tuberous sclerosis is not necessarily known[8]. In patients with Li-Fraumeni syndrome, radiotherapy should be avoided to the possible extent[9].

7. Drug therapy

There have recently been reports of several molecular-targeted agents effective for treating brain and nervous system tumors in patients with hereditary cancer syndromes. Everolimus, an mTOR inhibitor, was shown to reduce SEGA tumors by ≥50% in 35% of patients with tuberous sclerosis complex (TSC)[10]. Based on this finding, everolimus was covered by insurance in Japan in 2012. Bevacizumab, an anti-VEGF antibody, was shown to reduce acoustic neurilemoma by ≥20% in 6 of 10 patients with NF2 and to improve hearing in 4 of 7 patients undergoing hearing tests[11]. The administration of belzutifan, an HIF2α inhibitor, showed a tumor response rate of 30% in patients with VHL disease[12]. Also, a study administered selumetinib, an MEK inhibitor, to 50 pediatric patients with NF1, which showed a tumor response rate of 70% in patients with inoperable plexiform neurofibromas[13]. Among these four drugs, only everolimus and selumetinib (for pediatric use) are covered by insurance in Japan, as of August 2024.

■ References

1) Kratz CP, Achatz MI, Brugières L, et al. Cancer Screening Recommendations for Individuals with Li-Fraumeni Syndrome. Clin Cancer Res. 2017; 23(11):e 38-e45.[PMID: 28572266].
2) Yoshida Y, Kuramochi R, Ota Y, et al; Committee for the Revision of Guidelines for the Treatment of Neurofibromatosis Type 1. Neurofibromatosis type 1 (Recklinghausen's disease) practice guideline 2018. journal of the Japanese Dermatological Association. 2018; 128(1): 17-34.
3) Halliday D, Emmanouil B, Evans DGR. Updated protocol for genetic testing, screening and clinical management of individuals at risk of NF2-related Clin Genet. 2023;103(5):540-52. [PMID: 36762955].
4) Daniels AB, Tirosh A, Huntoon K, et al. Guidelines for surveillance of patients with von Hippel-Lindau disease: consensus statement of the International VHL Surveillance Guidelines Consortium and VHL Alliance. Cancer. 2023;129(19):2927-40.
5) Northrup H, Aronow ME, Bebin EM, et al. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Pediatr Neurol. 2021; 123: 50-66. [PMID: 34399110].
6) Grant-in-Aid for Health and Labour Sciences, Research Project for Intractable Disease Policy, "Comprehensive Research Group for Investigation of Actual Conditions, Construction of Clinical Practice System and Improvement of QOL in von Hippel-Rindow Disease". Von Hippel-Gentian Disease Clinical Practice Guide (2024 Edition). 2024.
(7) Health and Labour Science Research Grants-in-Aid for Intractable Diseases Policy Research Project, "Establishment of Clinical Practice Guidelines Based on Scientific Evidence through Cross-

Departmental Examination of Neurocutaneous Syndrome" Research Group. Neurofibromatosis type 2 (NF2) treatment guidelines (revised October 2016). 2016.
Subendocallosal Giant Cell Astrocytoma (SEGA) Clinical Practice Guideline Development Group. 2. Pediatric Brain Tumors Subendocallosal Giant Cell Astrocytoma (SEGA). Japanese Brain Tumor Society, Japanese Neurosurgical Society (ed. Brain Tumor Clinical Practice Guidelines 2019, 2nd Edition. 2019.
(9) Pediatric Hereditary Tumor Group Guideline Development Committee. Guidelines for the treatment of Leigh-Fraumeni syndrome, 2019 edition ver. 1.1. 2020. https://minds.jcqhc.or.jp/common/wp-content/plugins/pdfjs-viewer-shortcode/pdfjs/web/viewer.php?file=https://minds.jcqhc.or.jp/common/summary/pdf/c00607.pdf&dButton=false&pButton=false&oButton=false&sButton=true#zoom=auto&pagemode=none& amp;_wpnonce=3b871a512b (reference 2024-08-26)
10) Franz DN, Belousova E, Sparagana S, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2013;381(9861):125-32.
11) Plotkin SR, Stemmer-Rachamimov AO, Barker FG 2nd, et al. Hearing improvement after bevacizumab in patients with neurofibromatosis type 2. N Engl J Med. 2009; 361(4):358-67: 19587327]
12) Jonasch E, Donskov F, Iliopoulos O, et al. Belzutifan for Renal Cell Carcinoma in von Hippel-Lindau Disease. N Engl J Med. 2021;385(22):2036-46. PMID: 34818478]
(13) Gross AM, Wolters PL, Dombi E, et al. Selumetinib in Children with Inoperable Plexiform Neurofibromas. N Engl J Med. 2020; 382(15): 1430-42.[PMID: 32187457]

2. Pituitary gland

Hereditary cancer syndromes associated with pituitary tumors include multiple endocrine neoplasia type 1 (*MEN1*).

1. Overview

Clinically important hereditary cancer syndromes that cause pituitary tumors include multiple endocrine neoplasia type 1. In addition to *MEN1*, some genes (*AIP, GPR101, CDH23*) are known to be causative of hereditary pituitary tumors, all of which are rare.

2. Surveillance methods

In patients with multiple endocrine neoplasia type 1 (MEN1), surveillance of the pituitary gland is performed with hormone measurements and pituitary MRI examination. Many functional pituitary tumors associated with MEN1 are prolactin (PRL)-producing or growth hormone (GH)-producing tumors. Because blood GH concentrations fluctuate widely within a day, surveillance involves the measurement of PRL and insulin-like growth factor 1 (IGF-1, also known as somatomedin C), which reflects GH production, in addition to PRL measurement.

3. Starting age of surveillance

In patients with MEN1, it is recommended that pituitary surveillance be started at the age of 5 years[1)]. However, a report has suggested that the surveillance may be delayed until the mid-teens because of the low incidence rate of the disease before adolescence and its mostly asymptomatic nature even after the onset[2)].

4. Surveillance intervals

Hormone measurements should be performed every year, and pituitary MRI examination should be performed every 3 years if no tumor is found.

5. Surgical treatment

GH-producing tumors are treated with transsphenoidal pituitary tumor resection. Non-functioning tumors are indicated for surgery if headache, visual field constriction, or other symptoms are present, while follow-up is recommended for asymptomatic small tumors (<1 cm in diameter).

6. Drug therapy

Cabergoline, a dopamine agonist, is the first treatment of choice for PRL-producing tumors. Tumors that cannot be controlled with drug therapy are indicated for surgical treatment. For the purpose of suppressing hormone production, somatostatin derivatives (octreotide, lanreotide, and pasireotide) are used for GH-producing tumors that could not be cured by surgery.

■ References

1) Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012;97(9):2990-3011. [PMID: 22723327]
2) Manoharan J, Raue F, Lopez CL, et al. Is Routine Screening of Young Asymptomatic MEN1 Patients Necessary? World J Surg. 2017;41(8):2026-32. [PMID: 28321559]

3. Eyes

Hereditary cancer syndromes with a high lifetime risk of developing eye tumors (as well as their causative genes) include hereditary retinoblastoma (*RB1*), von Hippel–Lindau disease (*VHL*), tuberous sclerosis (*TSC1, TSC2*), neurofibromatosis type 1 (*NF1*), Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*), and individuals who carry a germline pathogenic variant (GPV) in *BAP1*.

1. Overview

Hereditary retinoblastoma occurs in individuals carrying GPV in *RB1*. Although its penetration rate differs depending on the variant, there is no clear difference in the properties of the tumors (malignant grade, treatment response, etc.)[1] (Many cases show a penetration rate of ≥90%, but missense mutations and changes outside the pocket domain tend to have a low penetration rate and a low tumor incidence.).

Retinal hemangioma occurs in 40–70% of patients with VHL disease, and approximately half of them develop retinal hemangioma in both eyes[2].

Retinal hamartoma occurs in approximately 40% of patients with tuberous sclerosis, and its differentiation from retinoblastoma can be problematic in some cases. Its diagnosis is made by fundus examination. Retinal hamartoma does not usually grow in size, and there is not much need for its long-term follow-up[3].

A small percentage of patients with Lynch syndrome develop sebaceous gland tumors of the eyelid, the condition of which is called Muir–Torre syndrome. Its diagnosis is made by slit-lamp microscopy and confirmed by pathology. It was reported that 9.2% of patients with Lynch syndrome developed skin tumors[4].

Some patients with familial adenomatous polyposis have congenital hypertrophy of the retinal pigmented epithelium (CHRPE)[5], but they do not require surveillance as it causes no visual impairment and does not become malignant.

Individuals carrying GPV in *BAP1* are at risk of developing uveal malignant melanoma[6].

2. Surveillance methods

Retinal tumors in patients with retinoblastoma are detected by fundus examination[1]. Observation of the peripheral retina is necessary for both eyes, and fundus examination under general anesthesia (EUA) is widely performed in overseas countries. In Japan, fundus examination is performed without anesthesia at many facilities due to constraints of the insurance and medical care systems. Brain MRI is performed for the surveillance of trilateral retinoblastoma, which is a related tumor[7]. No surveillance has been established for secondary cancers, although whole-body MRI is performed at some facilities overseas[8].

3. Starting age of surveillance

In patients with retinoblastoma, surveillance of eye tumors and trilateral retinoblastoma should be started at birth or upon identification of GPV. Some suggest that MRI for secondary cancers should be performed after the age of 8 years, which is the age when the examination can be performed without sedation[8].

In patients with VHL disease, fundus examination should be started at the age of 0 years[9].

4. Surveillance intervals

In patients with retinoblastoma, fundus examination should be performed without sedation every 2–4 weeks until the age of 8 weeks. EUA should be performed monthly until the age of 1 year, every 2 months until the age of 2 years, every 3 months until the age of 3 years, every 4 months until the age of 4 years, and every 6 months until the age of 5 years. Then, examination without sedation should be performed every 6 months until the age of 7 years[8]. For surveillance of trilateral retinoblastoma, MRI is recommended at the time of the diagnosis of eye tumors and every 6 months until the age of 5 years[7]. Some facilities perform whole-body MRI for secondary cancers yearly, although there is no consensus[8].

Regular annual checkups are recommended for patients with VHL disease[9].

5. Prevention

No method has been established for preventing the development of eye tumors in patients with hereditary retinoblastoma. To prevent the development of secondary cancers, it is recommended that the use of external radiation be avoided in the treatment of eye tumors and that smoking be stopped[10].

Similarly, no preventive method has been established for patients with VHL disease.

■ References

1) Shigenobu Suzuki, Takaaki Yanagisawa. Retinoblastoma. In: Japanese Society of Pediatric Hematology and Cancer, ed. Guidelines for the Treatment of Childhood Cancer, 2016 Edition. Kanehara Publishing Co.2016, 153-97.

(2) van Leeuwaarde RS, Ahmad S, van Nesselrooij B, et al. von Hippel-Lindau Syndrome. in Adam MP, Feldman J, Mirzaa GM, et al (eds). GeneReviews ® [Internet], Seattle (WA): University of Washington May 17, 2000 [Last revision: Feb 29, 2024]. https://www.ncbi.nlm.nih.gov/books/NBK1463/ (accessed 2024-08-26)

3) Rowley SA, O'Callaghan FJ, Osborne JP. Ophthalmic manifestations of tuberous sclerosis: a population based study. Br J Ophthalmol. 2001;85(4):420-3. [PMID: 11264130].

4) Zhong CS, Horiguchi M, Uno H, et al. Clinical factors associated with skin neoplasms in individuals with Lynch syndrome in a longitudinal J Am Acad Dermatol. 2023;88(6):1282-90. [PMID: 36773823].

5) Bisgaard ML, Bülow S. Familial adenomatous polyposis (FAP): genotype correlation to FAP phenotype with osteomas and sebaceous cysts. Am J Med Genet A. 2006;140(3):200-4[. PMID: 16411234]

6) Rai K, Pilarski R, Cebulla CM, et al. Comprehensive review of BAP1 tumor predisposition syndrome with report of two new cases. Clin Genet. 2016; 89(3): 285-294.[PMID: 26096145].

7) Rodjan F, de Graaf P, Brisse HJ, et al. Trilateral retinoblastoma: neuroimaging characteristics and value of routine brain screening on admission. Neurooncol. 2012;109(3):535-44: 22802019]

8) Skalet AH, Gombos DS, Gallie BL, et al. Screening Children at Risk for Retinoblastoma: Consensus Report from the American Association of Ophthalmic Oncologists and Pathologists. ophthalmology. 2018;125(3):453-8.[PMID: 29056300].

9) Grant-in-Aid for Health and Labour Sciences, Research Project for Intractable Disease Policy, "Comprehensive Research Group for Investigation of Actual Conditions, Construction of Clinical Practice System and Improvement of QOL in von Hippel-Rindow Disease". Von Hippel-Rindow Disease Clinical Practice Guide (2024 Edition). 2024.

10) Foster MC, Kleinerman RA, Abramson DH, et al. Tobacco use in adult long-term survivors of retinoblastoma. Cancer Epidemiol Biomarkers Prev. 2006; 15 (8): 1464-8. [PMID: 16896033].

4. Thyroid and parathyroid glands

Hereditary cancer syndromes with a high lifetime risk of developing thyroid cancer (as well as their causative genes) include multiple endocrine neoplasia type 2 (*RET*), familial adenomatous polyposis (familial polyposis coli) (*APC*), Cowden syndrome/*PTEN* hamartoma tumor syndrome (*PTEN*), and *DICER1* syndrome (*DICER1* tumor predisposition) (*DICER1*). In addition, hereditary tumor syndromes with a high lifetime risk of developing parathyroid tumors include multiple endocrine neoplasia types 1 and 2 (*MEN1, RET*).

1. Overview

Clinically important diseases of hereditary thyroid cancer include medullary thyroid carcinoma associated with multiple endocrine neoplasia type 2 (MEN2). Medullary thyroid carcinoma occurs in all patients with MEN2, and approximately 30% of all medullary thyroid carcinomas are associated with MEN2. MEN2 is classified by phenotype; MEN2A is characterized by the development of medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism, while MEN2B is characterized by the development of medullary thyroid carcinoma, pheochromocytoma, symptoms of Marfan syndrome, mucosal neuroma of the tongue and lips, and intestinal neuroganglioma. Although MEN2 that exhibits the occurrence of only medullary thyroid carcinoma within a family may be distinguished from familial medullary thyroid carcinoma (FMTC), it is considered to be a subtype of MEN2A. *RET*, the causative gene of MEN2, is an oncogene and shows a clear genotype-phenotype correlation. Therefore, the disease requires variant-specific responses.

Hereditary tumor syndromes involving thyroid cancer as a partial symptom include familial adenomatous polyposis and Cowden syndrome/*PTEN* hamartoma tumor syndrome.

Hereditary hyperparathyroidism occurs in patients with multiple endocrine neoplasia type 1 (MEN1) or MEN2A. Most patients develop hyperplasia, and cancers are rare. It occurs in nearly all patients with MEN1 and often as the initial lesion. It does not have a high penetration rate in patients with MEN2A (approximately 10%). Also, hyperparathyroidism-jaw tumor syndrome (HPT-JT), which is a combination of hyperparathyroidism and jaw tumors, is known to occur, and approximately 15% of parathyroid lesions associated with HPT-JT are cancers.

2. Surveillance methods

Surveillance of the thyroid gland is performed mainly with thyroid ultrasonography and palpation. Serum calcitonin and carcinoembryonic antigen (CEA) serve as useful tumor markers for medullary thyroid carcinoma.

Surveillance of the parathyroid gland is performed with the measurements of serum calcium and parathyroid hormone (intact PTH). Imaging diagnosis is performed when considering surgery after the disease onset, but it is not highly useful as a means of surveillance.

3. Starting age of surveillance

According to the guidelines released by the U.S. American Thyroid Association, prophylactic total thyroidectomy is recommended in infancy for patients carrying GPV at amino acid codon 918 of *RET* (nearly all patients with MEN2B) and before the age of 5 years for patients carrying GPV at amino acid codon 634 of *RET* (approximately 50% of patients with MEN2A)[1]. Thus, surveillance should be started immediately after birth. Patients carrying GPV at other codons often develop medullary thyroid carcinoma after infancy, and it is acceptable to delay the start of surveillance until the patient reaches school age or later, based on discussion with the parents or guardians.

For MEN1 patients with hyperparathyroidism, many guidelines recommend starting surveillance of the parathyroid gland at the age of 5–8 years[2]. On the other hand, some suggest that surveillance may be delayed until the mid-teens because of its low incidence rate before adolescence and its mostly asymptomatic nature even after the onset[3]. For patients with MEN2A, surveillance of the parathyroid gland should be started after school age.

In women with familial adenomatous polyposis, baseline ultrasonography should be started in the late teens (at intervals of 2–5 years if normal), and the interval should be shortened if there is a family history of thyroid cancer.

See Chapter 4 for responses specific to other gene.

4. Surveillance intervals

Surveillance is performed mainly with ultrasonography and biochemical tests, and because these are minimally invasive for patients, annual surveillance is generally recommended. Since papillary thyroid cancer associated with familial adenomatous polyposis has low malignancy and spontaneously regresses in some cases[4], it is generally considered appropriate to perform ultrasonography every 2–5 years after late adolescence.

5. Surgical treatment

Total thyroidectomy is an absolute indication for MEN2-associated medullary thyroid carcinoma, even if the lesion is small[1]. International guidelines recommend prophylactic total thyroidectomy for pediatric patients. In Japan, however, periodic surveillance is performed for children who carry GPV in *RET*, and total thyroidectomy is performed when the disease onset is confirmed based on the findings of imaging tests and serum calcitonin levels.

In patients with MEN1-associated hyperparathyroidism, the entire gland, including the normal gland, is removed, a portion of which is then autografted to the forearm or other parts of the body, or a subtotal parathyroidectomy is performed, leaving only a portion of the smallest gland. The former carries the risk of permanent hypoparathyroidism despite a low recurrence rate, while the latter has a high recurrence rate. When surgery is performed for MEN2-associated hyperparathyroidism, only the enlarged gland is removed, as it has a low penetration rate.

6. Drug therapy

Many probands with MEN2 have developed regional lymph node metastases or distant metastases by the time of diagnosis of medullary thyroid carcinoma, except for patients diagnosed in childhood through pre-onset diagnosis of blood relatives. However, because their progression is relatively slow depending on the GPV in *RET*, many patients are followed up without treatment. Currently, four drugs (vandetanib, sorafenib, lenvatinib, and selpercatinib) are covered by insurance for advanced cases.

The administration of calcium receptor agonists (cinacalcet and evocalcet) may be considered when surgery for parathyroid function is not selected or has a high risk in patients with MEN1[5].

■ References

1) Wells SA, Jr., Asa SL, Dralle H, et al; American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma. revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25(6):567-610.[PMID: 25810047].
2) Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). PMID: 22723327]
3) Manoharan J, Raue F, Lopez CL, et al. Is Routine Screening of Young Asymptomatic MEN1 Patients Necessary? World J Surg. 2017; 41(8):2026-32.[PMID: 28321559]
4) Uchino S, Ishikawa H, Miyauchi A, et al. Age-and Gender-Specific Risk of Thyroid Cancer in Patients With Familial Adenomatous Polyposis. J Clin Endocrinol Metab. 2016;101(12):4611-17.[PMID: 27623068].
5) Moyes VJ, Monson JP, Chew SL, et al. Clinical Use of Cinacalcet in MEN1 Hyperparathyroidism. Int J Endocrinol. 2010; 2010: 906163.[PMID: 20585352].

5. Mammary glands

Hereditary cancer syndromes with a high lifetime risk of developing breast cancer (as well as their causative genes) include narrowly defined hereditary breast and ovarian cancer (*BRCA1, BRCA2*), Li-Fraumeni syndrome (*TP53*), Cowden syndrome/*PTEN* hamartoma tumor syndrome (*PTEN*), neurofibromatosis type 1 (*NF1*), Peutz-Jeghers syndrome (*STK11*), hereditary diffuse gastric cancer (*CDH1*), and individuals who carry a germline pathogenic variant (GPV) in *PALB2*, *ATM*, *CHEK2*, *BARD1*, *BRIP1*, *RAD51C*, or *RAD51D*. Of these, genetic tests targeting only *BRCA1* and *BRCA2* (hereafter referred to as *BRCA1/2*) have been approved as devices under the Pharmaceutical and Medical Device Act in Japan.

1. Overview

The surgical procedure for the affected breast (total or partial resection) or contralateral risk-reducing mastectomy (CRRM) is considered in breast cancer surgery for patients who carry GPV in *BRCA1/2* (hereditary breast and ovarian cancer: HBOC). For breast cancer-free patients, surveillance should be started at the recommended age, and bilateral risk-reducing mastectomy should be considered. There is insufficient evidence for the onset prevention of breast cancer with antiestrogenic drugs. For *PALB2*, treatment similar to that for HBOC should be considered, as it has the second highest risk of breast cancer after *BRCA1/2*. If a patient with breast cancer is found to have GPV in *TP53*, total mastectomy is recommended for the purpose of avoiding secondary cancers associated with breast-sparing irradiation. For other cancer susceptibility genes with high breast cancer penetrance (*PTEN, NF1, STK11, CDH1*) and cancer susceptibility genes with medium to low penetrance (*ATM, CHEK2, BARD1, BRIP1, RAD51C, RAD51D*), there is insufficient evidence to recommend risk-reducing surgery, and the basis of their management is to start surveillance at the age recommended for each gene. A study of Japanese patients with breast cancer reported the GPV frequency for the above genes as follows: 1.45% for *BRCA1*, 2.71% for *BRCA2*, 0.23% for *TP53*, 0.40% for *PALB2*, 0.31% for *ATM*, 0.37% for *CHEK2*, 0.16% for *PTEN*, 0.11% for *NF1*, and 0.03% for *CDH1*[1].

2. Surveillance methods

Guidelines have specified annual mammography and contrast-enhanced breast MRI as the methods of breast surveillance[2, 3]. Breast ultrasonography, which is widely used in Japan, is safe and simple, but there has been no evidence of its usefulness for surveillance. Also, mammography or breast ultrasonography can be performed between annual contrast-enhanced breast MRI examinations, depending on the age and breast density (e.g., mammography or breast ultrasonography may be performed 6 months after contrast-enhanced breast MRI.)[4]. Secondary prevention aimed at the early

detection of breast cancer is also expected to be effective for men carrying GPV in *BRCA1/2*, and particularly for *BRCA2*, surveillance with mammography or breast ultrasonography is considered if the patient has a history of male breast cancer or gynecomastia. In addition, breast awareness (breast-conscious lifestyle habits) is recommended for both men and women.

3. Starting age of surveillance and its frequency (intervals)

The recommended starting age of surveillance differs depending on the gene[2]. See **Chapter 4** for details on gene-specific surveillance.

4. Chemoprevention

There is currently no evidence to recommend prophylactic endocrine therapy for reducing the risk of breast cancer onset in breast cancer-free patients carrying GPV in *BRCA1/2*[5]. Postoperative treatment with tamoxifen may suppress the development of contralateral breast cancer in breast cancer-affected patients who carry GPV in *BRCA1/2*, but the risk-reduction effect of CRRM offers more certainty[6]. The evidence for the preventive effect of raloxifene and aromatase inhibitors in patients carrying GPV in *BRCA1/2* is unclear[7]. Clinical studies have examined the preventive effect of denosumab in patients carrying GPV in *BRCA1*, but there is currently no evidence to recommend its administration as a new drug for preventing the development of breast cancer[3, 7].

5. Surgical treatment (risk-reducing surgery)

Regarding the mastectomy for breast cancer-affected patients who carry GPV in *BRCA1/2*, total resection is recommended over partial resection, considering the risk of developing new breast cancer in the spared breast after partial resection[3]. However, if the patient strongly desires partial resection, it is acceptable to select partial resection after the patient understands the risk of developing new breast cancer in the spared breast and the need for continuous surveillance, and it is important to support decisions made based on sufficient information[3, 8]. Although CRRM is certainly effective in reducing the risk of breast cancer onset in the contralateral breast, there is insufficient evidence of its effect in improving the survival rate. Its implementation should be considered by comprehensively taking into account the treatment and prognosis of existing breast cancer, the desire to breastfeed after childbirth, psychological effects, risk-reducing salpingo-oophorectomy (which has a clear effect of improving the survival rate), and other factors. When proposing CRRM, the uncertainty of the evidence should be considered, and the diversity of values should be taken into account. Medical professionals performing CRRM should consult not only with the patient but also with family members and collaboratively support their decision-making. CRRM should be performed at a facility that has a team-based medical care system capable of providing genetic counseling in addition to meeting the implementation standards. In HBOC, bilateral risk-reducing mastectomy for breast cancer-free individuals is also

certainly effective in reducing the risk of breast cancer onset in bilateral breasts. However, there is still uncertainty regarding its effect of improving the survival rate, since much evidence is influenced by risk-reducing salpingo-oophorectomy. Therefore, it is essential to provide adequate consultation at a well-equipped facility.

PALB2 has the second highest risk of breast cancer after *BRCA1/2*[9], and all international guidelines recommend its surveillance. However, there are differing opinions regarding the appropriateness of risk-reducing surgery[10].

If a breast cancer patient under 30 years of age is found to have no GPV in *BRCA1/2*, genetic testing (syndrome-specific genetic testing (SSGT) or MGPT) should be considered, keeping in mind the possibility of Li-Fraumeni syndrome (*TP53*)[11, 12]. If GPV is detected in *TP53*, total mastectomy is recommended for the purpose of avoiding secondary cancers associated with breast-sparing irradiation[8, 13]. Although international guidelines list contralateral risk-reducing surgery as an option to be discussed[2], there is little evidence to recommend risk-reducing surgery for cancer susceptibility genes causative of hereditary tumor syndromes (*PTEN*, *NF1*, *STK11*, *CDH1*) and genes with a medium to low penetration rate (*ATM*, *CHEK2*, *BARD1*, *BRIP1*, *RAD51C*, *RAD51D*). Therefore, a realistic response is to start surveillance at the age recommended by guidelines[2].

6. Drug therapy

In patients with HER2-negative breast cancer who carry GPV in *BRCA1/2*, the PARP inhibitor olaparib can be administered for the postoperative treatment of recurrent high-risk breast cancer, and the PARP inhibitors olaparib or talazoparib can be administered for the treatment of metastatic recurrent breast cancer if eligibility requirements are met, regardless of gender. In addition, the ESMO guidelines recommend PARP inhibitors for individuals who carry GPV in *PALB2*[14]. Carboplatin, a platinum-based agent, is expected to be effective based on its mechanism of action and subgroup analysis of the HBOC population, and international guidelines recommend its use[14, 15]. A group of cancer susceptibility genes with medium to low penetrance of breast cancer risk (*ATM*, *CHEK2*, *BARD1*, *BRIP1*, *RAD51C*, *RAD51D*) encode factors (proteins) involved in homologous recombination repair (HRR) of DNA double-strand breaks, as with *BRCA1/2*. Therefore, PARP inhibitors may be effective for patients whose breast cancer tissue is in the state of homologous recombination deficiency (HRD), and clinical trials targeting individuals who carry GPV in these genes are being conducted[16]. If CGP detects alterations in these genes, they are examined as potential therapeutic targets, and if they are found to be germline findings (GPV/PGPV), their disclosure should be discussed by the expert panel. Depending on the situation, information should be provided about health management measures and genetic testing, including those for blood relatives, at genetic counseling sessions, and their implementation should be considered.

■ References

1) Momozawa Y, Iwasaki Y, Parsons MT, et al. Germline pathogenic variants of 11 breast cancer genes in 7,051 Japanese patients and 11,241 controls. Nat Commun. 2018;9(1):4083. [PMID: 30287823]
2) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic. Version 3. 2024. (accessed 2024-08-26)
3) Japan Organization of Hereditary Breast and Ovarian Cancer (ed.). Clinical Practice Guidelines for Hereditary Breast and Ovarian Cancer (HBOC), 2024 Edition. Kanehara Publishing Co., Ltd. 2024.
4) Sessa C, Balmaña J, Bober SL, et al. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes:ESMO Clinical Practice Guideline. Ann Oncol. 2023;34(1): 33-47. [PMID: 36307055]
5) Japanese Breast Cancer Society Clinical Practice Guidelines Committee. Clinical Practice Guidelines for Breast Cancer, 2022 Edition. Epidemiology and Diagnosis Edition. 2022. https://jbcs.xsrv.jp/guideline/2022/t/
6) Baildam AD. Current knowledge of risk reducing mastectomy: Indications, techniques, results, benefits, harms. Breast. 2019;46:48-51. [PMID: 31082761]
7) Singer CF. Nonsurgical Prevention Strategies in BRCA1 and BRCA2 Mutation Carriers. Breast Care (Basel). 2021;16(2):144-8. [PMID: 34012368]
8) Tung NM, Boughey JC, Pierce LJ, et al. Management of Hereditary Breast Cancer: American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology Guideline. J Clin Oncol. 2020;38(18):2080-106. [PMID: 32243226]
9) Dorling L, Carvalho S, Allen J, et al.;Breast Cancer Association Consortium. Breast Cancer Risk Genes-Association Analysis in More than 113,000 Women. N Engl J Med. 2021;384(5): 428-39. [PMID: 33471991]
10) Corso G, Robson ME, Sacchini V. Points to Consider Regarding Risk-Reducing Mastectomy in High-, Moderate-, and Low-Penetrance Gene Carriers. Ann Surg Oncol. 2022;29(9):5821-5. [PMID: 35604619]
11) McCuaig JM, Armel SR, Novokmet A, et al. Routine TP53 testing for breast cancer under age 30: ready for prime time? Fam Cancer. 2012;11(4):607-13. [PMID: 22851211]
12) Pediatric Hereditary Tumor Research Group Guideline Creation Committee. Clinical Practice Guidelines for Li-Fraumeni Syndrome, 2019 Edition. ver. 1.1. 2020. https://minds.jcqhc.or.jp/common/wp-content/plugins/pdfjs-viewer-shortcode/pdfjs/web/viewer.php?file=https://minds.jcqhc.or.jp/common/summary/pdf/c00607.pdf&dButton=false&pButton=false&oButton=false&sButton=true#zoom=auto&pagemode=none&_wpnonce=3b871a512b (reference 2024-08-26)

13) Japanese Breast Cancer Society Clinical Practice Guidelines Committee. Review 2: Cases for which radiotherapy is not recommended after breast surgery. Japanese Breast Cancer Society (ed.). Clinical Practice Guidelines for Breast Cancer, 2022 Edition, Treatment Edition, 2022. https://jbcs.xsrv.jp/guideline/2022/h_index/s2/ (reference 2024-08-26)

14) Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021;32(12):1475-95 [PMID: 34678411]

15) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer. Version 5, 2024.

16) Graffeo R, Rana HQ, Conforti F, et al. Moderate penetrance genes complicate genetic testing for breast cancer diagnosis: ATM, CHEK2, BARD1 and RAD51D. Breast. 2022;65:32-40. [PMID: 35572246]

6. Lungs

Hereditary cancer syndromes with a high lifetime risk of developing lung cancer (as well as their causative genes) include Li-Fraumeni syndrome (*TP53*), Peutz-Jeghers syndrome (*STK11*), and individuals who carry a germline pathogenic variant (GPV) in *EGFR*, *HER2*, *CDK4*, or *CDKN2A*. Patients with *DICER1* syndrome (*DICER1* tumor predisposition) (*DICER1*) carry a high lifetime risk of developing pleuropulmonary blastoma, which is observed in infancy (→See Chapter: Children). Patients with Birt-Hogg-Dubé (BHD) syndrome (*FLCN*), although it does not involve malignant tumors, carry an increased risk of developing pulmonary cysts and spontaneous pneumothorax. Patients with tuberous sclerosis (*TSC1*/ *TSC2*) carry an increased risk of developing lymphangioleiomyomatosis (LAM). Among juvenile polyposis syndromes, many individuals carrying GPV in *SMAD4* develop hereditary hemorrhagic telangiectasia (HHT), which increases the risk of developing pulmonary arteriovenous malformation.

1. Overview

Although lung cancer is not a core tumor in Li-Fraumeni syndrome, the lifetime risk of developing lung cancer among patients with Li-Fraumeni syndrome is estimated to be 2–7%[1]. In addition, a prospective observational study showed that 5 (4.7%) of 107 patients with Li-Fraumeni syndrome developed lung adenocarcinoma during the 5-year study period[2]. Therefore, patients with Li-Fraumeni syndrome require surveillance for lung cancer.

Individuals who carry an active germline variant in the tyrosine kinase domain (codons 685–953) of *EGFR* are at high risk of developing lung cancer. A five-generation study of families carrying *EGFR* T790M showed that 19 (65.5%) of 29 GPV carriers developed lung cancer[3]. It has also been reported that GPV carriers of *EGFR* T790M account for 0.3–0.9% of patients with non-squamous non-small cell lung cancer[4]. A prospective observational study reported that 55% of GPV carriers of *EGFR* T790M, R776H, or G724S developed lung cancer and that second hits were found in 95% of their tumor cells[3]. This suggests that although *EGFR* is an oncogene, second hits are necessary for the development of lung cancer, as in tumor suppressor genes. In addition, families with familial lung adenocarcinoma lineage carrying *HER2* G660D have been reported in the Japanese population.

Genetic testing revealed that 14.9% of lung cancer patients had GPV in the following causative genes: *BRCA2* (2.8%), *CHEK2* (2.1%), *ATM* (1.9%), *TP53* (1.3%), *BRCA1* (1.25%), and *EGFR* (1%)[5]. In addition, germline WES showed that 43.7% of 87 patients with small cell lung cancer harbored a total of 42 GPVs in 35 cancer susceptibility genes, including *RAD51D*, *CHEK1*, *BRCA2*, and *MUTYH*[6].

Pleuropulmonary blastoma in *DICER1* syndrome is mainly divided into types I, II, and III. More than 80% of patients with type I develop the disease at the age of ≤1 year (mainly at the age of 0 years), while

approximately 90% patients with type II or III develop the disease at the age of 1–4 years, with a peak at the age of 2–3 years[7].

Patients with BHD syndrome have the problem of repetitive spontaneous pneumothorax due to multiple pulmonary cysts. Also, LAM associated with tuberous sclerosis progresses slowly with the formation of multiple cysts in the lungs. The progression of pulmonary lesions results in repeated pneumothoraces, and respiratory failure occurs due to decreased respiratory function.

2. Surveillance methods

Surveillance for lung cancer is generally performed with chest CT examination, for which the use of thin slices is desirable. In patients with Li-Fraumeni syndrome, however, exposure to radiation may increase the risk of tumor development, and thus, diagnostic and therapeutic radiation should be avoided or minimized to the possible extent. For this reason, surveillance with whole-body MRI examination is recommended for patients with Li-Fraumeni syndrome.

3. Starting age of surveillance and surveillance intervals

Annual whole-body MRI examination is recommended for patients with Li-Fraumeni syndrome at all ages[8].

Diagnosis of blood relatives and pulmonary surveillance have been proposed for individuals carrying *EGFR* T790M starting at the age of 20 years, but there is no established surveillance method. In a prospective observational study of individuals carrying GPV in *EGFR*, pulmonary nodules were identified in 9 (60%) of 15 patients who underwent CT examination, and their nodules exhibited no growth for a long period of time, as early as in their 30s, suggesting the possibility of adenocarcinoma in situ[3]. In patients with *DICER1* syndrome, surveillance for pleuropulmonary blastoma is performed every 4–6 months since they are young children. It may also be detected by prenatal ultrasonography.

4. Chemoprevention

There are no known drugs effective in preventing the development of lung cancer, and among lifestyle habits, smoking poses a risk.

5. Surgical treatment

Lung cancer that carries a hereditary risk is surgically treated in the same manner as that for sporadic lung cancer. The surgical approach (extent of lung resection) is determined based on the extent of disease progression and physiological findings, including respiratory and circulatory functions. In principle, *DICER1* syndrome patients with type I pleuropulmonary blastoma are expected to have a favorable prognosis with surgical resection alone. *DICER1* syndrome patients with type II or III pleuropulmonary blastoma usually undergo surgical resection and chemotherapy, but those who have

metastases at the time of diagnosis have a poor prognosis[7]. Pneumothorax in patients with BHD syndrome is surgically treated in the same manner as general surgery for spontaneous pneumothorax. Invasive treatment, including pleurodesis, may be considered for patients who experience repeated pneumothoraces due to tuberous sclerosis-associated LAM, while lung transplantation is indicated for patients who have developed respiratory failure due to the progression of pulmonary lesions. For HHT-associated pulmonary arteriovenous malformation, early intervention is desirable if it has a size of ≥2–3 cm or an inflow artery diameter of ≥3 mm, and embolization by interventional radiology (IVR) or surgical resection is performed.

6. Drug therapy

For unresectable locally advanced non-small cell lung cancer and limited stage small cell lung cancer, chemoradiotherapy is optimal if curative irradiation is indicated, and chemotherapy is the preferred treatment if it is metastatic cancer. However, there are no specific recommendations for patients with Li-Fraumeni syndrome, and their treatment is determined based on the Clinical Practice Guidelines for Lung Cancer[9]. Tuberous sclerosis-associated LAM is treated with an mTOR inhibitor (sirolimus).

■ References

1) McBride KA, Ballinger ML, Killick E, et al. Li-Fraumeni syndrome: cancer risk assessment and clinical management. Nat Rev Clin Oncol. 2014; 11(5):260 -71.[PMID: 24642672].
2) Caron O, Frebourg T, Benusiglio PR, et al. Lung Adenocarcinoma as Part of the Li-Fraumeni Syndrome Spectrum: Preliminary Data from the LIFSCREEN Randomized Clinical Trial. jAMA Oncol. 2017; 3(12):1736-7.[PMID: 28772306].
3) Oxnard GR, Chen R, Pharr JC, et al. Germline *EGFR* Mutations and Familial Lung Cancer. J Clin Oncol. 2023;41(34):5274-84.[PMID: 37579253].
4) Benusiglio PR, Fallet V, Sanchis-Borja M, et al. Lung cancer is also a hereditary disease. Eur Respir Rev. 2021;30(162):210045.[PMID: 34670806]
5) Sorscher S, LoPiccolo J, Heald B, et al. Rate of Pathogenic Germline Variants in Patients With Lung Cancer. JCO Precis Oncol. 2023;7:e2300190.[PMID: 37992258]
6) Tlemsani C, Takahashi N, Pongor L, et al. Whole-exome sequencing reveals germline-mutated small cell lung cancer subtype with favorable response to Sci Transl Med. 2021;13(578):eabc7488.
7) Nakano Y, Kato M. Genetic testing and surveillance for *Dicer1* syndrome. Genetic Tumors. 2023; 22 (3) : 61-7.
8) Schneider K, Zelley K, Nichols KE, et al. Li-Fraumeni Syndrome. Adam MP, Feldman J, Mizaa GM, et al (. eds): GeneReviews® [Internet], Seattle (WA): University of Washington Jan 19, 1999 [Last update: Nov 21, 2019].
https://www.ncbi.nlm.nih.gov/books/NBK1311/

9) Japan Lung Cancer Society. Guidelines for Lung Cancer Treatment - Including Malignant Malignant Pleural Mesothelioma and Thymic Tumors - 2022 Edition, 7th Edition. 2023.

7. Stomach and duodenum

Hereditary tumor syndromes with a high lifetime risk of developing gastric cancer (as well as their causative genes) include hereditary diffuse gastric cancer (*CDH1*), Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*), familial adenomatous polyposis (familial polyposis coli) (*APC*), Peutz-Jeghers syndrome (*STK11*), juvenile polyposis syndrome (*SMAD4, BMPR1A*), Cowden syndrome/*PTEN* hamartoma tumor syndrome (*PTEN*), Li-Fraumeni syndrome (*TP53*), hereditary breast and ovarian cancer (*BRCA1, BRCA2*), and individuals who carry a germline pathogenic variant (GPV) in *ATM* or *PALB2*. Also, patients with Lynch syndrome or familial adenomatous polyposis carry a high lifetime risk of developing duodenal cancer, in addition to gastric cancer.

1. Overview

Hereditary gastric cancer has a distinctive histological type of gastric cancer caused by the causative genes. Signet-ring cell carcinoma is common in patients with hereditary diffuse gastric cancer, while intestinal (differentiated) gastric cancer is common in patients with Lynch syndrome, with a particularly high frequency among those carrying GPV in *MLH1* or *MSH2*. The risk of developing gastric cancer among patients with Lynch syndrome is higher in East Asia, including Japan, than in Europe and the United States; one of the reasons is likely the involvement of *Helicobacter pylori* (*H. pylori*) infection, as in sporadic gastric cancer. Also, a high rate of *H. pylori* infection has been reported in Japanese gastric cancer-affected patients with Lynch syndrome, and screening for *H. pylori* infection is recommended for patients with Lynch syndrome for the purpose of reducing the risk of gastric cancer. The involvement of *H. pylori* infection in the development of gastric cancer has also been reported in individuals who carry GPV in HRR genes, including *BRCA1, BRCA2, ATM*, and *PALB2*, and it is thought that impaired repair of DNA damage caused by *H. pylori* infection increases the risk of gastric cancer[1]. On the other hand, a negative correlation between *H. pylori* infection and the development of fundic gland polyposis has been observed in patients with familial adenomatous polyposis, but they may develop tumorous lesions, such as adenomas and carcinomas, regardless of the presence or absence of fundic gland polyposis. In addition, no method of upper gastrointestinal surveillance has been established because there have been few reported cases of gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), whose main symptom is fundic gland polyposis. However, upper gastrointestinal surveillance is important due to the high risk of developing gastric cancer.

Patients with Lynch syndrome or familial adenomatous polyposis carry a high risk of developing duodenal cancer. In particular, those with familial adenomatous polyposis tend to develop multiple duodenal adenomas, which are precancerous lesions, even in the papillary region.

2. Surveillance methods

For individuals carrying GPV in genes related to hereditary gastric and duodenal cancers, upper gastrointestinal surveillance is performed with upper gastrointestinal endoscopy. If it is necessary to observe the anal side of the horizontal part of the duodenum, the use of a small-diameter colonoscope, capsule endoscope, or balloon endoscope should also be considered. In patients with familial adenomatous polyposis or juvenile polyposis syndrome, polyposis may coexist in the background gastric mucosa, requiring careful observation to avoid overlooking cancer. Since the endoscopic findings of hereditary diffuse gastric cancer or gastric cancer occurring in patients with Li-Fraumeni syndrome may only show slight changes in color, narrow band imaging should be used in addition to white-light imaging. It is recommended to endoscopically resect adenomas and intramucosal carcinomas detected by upper gastrointestinal endoscopy[2]. Also, deep duodenal imaging should be performed to the extent possible in patients with Lynch syndrome or familial adenomatous polyposis, who are at high risk of developing duodenal cancer. In addition, referral to a specialized facility should be considered if endoscopic treatment of lesions is difficult or if endoscopic treatment of duodenal adenomas is considered.

3. Screening test for *Helicobacter pylori* infection and eradication therapy

Eradication of *H. pylori* infection is recommended for patients in their 20s with hereditary diffuse gastric cancer if they do not wish to undergo prophylactic total gastrectomy[3].

A high rate of *H. pylori* infection has been reported in Japanese gastric cancer-affected patients with Lynch syndrome. Thus, screening for *H. pylori* infection is recommended for patients with Lynch syndrome for the purpose of reducing the risk of gastric cancer, and if *H. pylori* infection is detected, its eradication should be considered[2, 4].

The involvement of *H. pylori* infection in the development of gastric cancer has also been reported in individuals who carry GPV in HRR genes, and it is thought that impaired repair of DNA damage caused by *H. pylori* infection increases the risk of gastric cancer[1].

4. Starting age of surveillance

For individuals carrying GPV in genes related to hereditary gastric and duodenal cancers, the starting age of upper gastrointestinal surveillance has been proposed according to the risk of developing gastric and duodenal cancers.

In patients with hereditary diffuse gastric cancer, upper gastrointestinal surveillance should be started in the teenage years or 5–10 years earlier than the age of the youngest affected member of the family (see the section of “Prophylactic total gastrectomy” below). For patients with Lynch syndrome, it is recommended that upper gastrointestinal surveillance be started at the age of 30–35 years[5]. In particular, this is considered for individuals at high risk of developing gastric cancer, such as those who

have been infected with *H. pylori*, as well as individuals with a family history of gastric or duodenal cancer. For patients with familial adenomatous polyposis, upper gastrointestinal surveillance should be started at the age of 20–25 years, but upper gastrointestinal endoscopy should also be considered at the time of diagnosis of familial adenomatous polyposis or before colorectal surgery. For patients with Peutz-Jeghers syndrome, upper gastrointestinal endoscopy is recommended at the age of 8 years[6, 7]. Upper gastrointestinal surveillance should be started at the age of 10 years for patients with juvenile polyposis syndrome[8] and at the age of 15 years for patients with Cowden syndrome/*PTEN* hamartoma tumor syndrome[9]. In patients with Li-Fraumeni syndrome, upper gastrointestinal surveillance should be started in the 20s, but consideration should also be given to starting upper gastrointestinal surveillance 5–10 years earlier than the age of the youngest affected member of the family.

5. Surveillance intervals

In individuals carrying GPV in genes related to hereditary gastric and duodenal cancers, upper gastrointestinal surveillance should be performed at intervals of 1–2 (3) years.

In patients with hereditary diffuse gastric cancer, it is recommended that upper gastrointestinal surveillance with upper gastrointestinal endoscopy (including random biopsy) be performed every 6–12 months if total gastrectomy is not selected[3, 10-13]. In addition, upper gastrointestinal surveillance should be performed for patients with Lynch syndrome every 1–3 years.

For patients with familial adenomatous polyposis, the intervals of upper gastrointestinal surveillance have been proposed based on the modified Spigelman classification for duodenal adenomas and carcinomas; upper gastrointestinal surveillance at intervals of 2–5 years is recommended for Stage 0 to III patients, while upper gastrointestinal surveillance by a specialist at intervals of 6 months to 1 year is recommended for Stage IV patients.

Responses for patients with juvenile polyposis syndrome vary depending on the number of polyps and phenotype, and it is recommended that upper and lower gastrointestinal endoscopy be performed every 1–3 years.

6. Prophylactic total gastrectomy

Regarding prophylactic total gastrectomy for hereditary diffuse gastric cancer, responses vary depending on guidelines, thereby requiring careful consideration; some guidelines suggest that decision-making be supported through the presentation of the options of total gastrectomy and endoscopic surveillance after considering the patient's preferences[2], while others recommend that total gastrectomy be performed in all patients regardless of the findings of upper gastrointestinal endoscopy[10], or that total gastrectomy be performed in patients with a family history of hereditary diffuse gastric cancer[3]. For patients with juvenile polyposis syndrome, gastrectomy should be considered if polyp-related symptoms (e.g., anemia, vomiting, and hypoproteinemia) or malignant findings cannot be controlled

endoscopically[5]. There has been no evidence to support the use of prophylactic total gastrectomy for individuals carrying GPV in other genes related to hereditary gastric cancer.

■ References

1) Usui Y, Taniyama Y, Endo M, et al. Helicobacter pylori, Homologous-Recombination Genes, and Gastric Cancer. N Engl J Med. 2023;388(13):1181-90. [PMID: 36988593]
2) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024. (accessed 2024-08-26)
3) Blair VR, McLeod M, Carneiro F, et al. Hereditary diffuse gastric cancer:updated clinical practice guidelines. Lancet Oncol. 2020;21(8):e386-97. [PMID: 32758476]
4) Japanese Society for Cancer of the Colon and Rectum (ed.). Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition. Kanehara Publishing Co., Ltd.
5) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment:Breast, Ovarian and Pancreatic. Version 3. 2024. (accessed 2024-08-26)
6) Yamamoto H, Abe T, Ishiguro S, et al. Clinical Practice Guidelines for Peutz-Jeghers Syndrome in Children and Adults (2020 Edition). Journal of Hereditary Tumors. 2020;20(2):59-78.
7) McGarrity TJ, Amos CI, Baker MJ. Peutz-Jeghers Syndrome. Adam MP, Feldman J, Mirzaa GM, et al (eds). GeneReviews® [Internet], Seattle (WA): University of Washington Feb 23, 2001 [Last update: Sep 2, 2021].
https://www.ncbi.nlm.nih.gov/books/NBK1266/ (accessed 2024-08-26)
8) Matsumoto T, Arai M, Iwama T, et al. Clinical Practice Guidelines for Juvenile Polyposis Syndrome in Children and Adults (2020 Edition). Journal of Hereditary Tumors. 2020;20(2):79-92.
9) Takayama T, Igarashi M, Ohsumi S, et al. Clinical Practice Guidelines for Cowden Syndrome/*PTEN* Hamartoma Tumor Syndrome in Children and Adults (2020 Edition). Journal of Hereditary Tumors. 2020;20(2):93-114.
10) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Gastric Cancer. Version 2. 2023.
11) Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015;110(2):223-62; quiz 263. [PMID:25645574]
12) Kaurah P, Huntsman DG. Hereditary Diffuse Gastric Cancer. In Adam MP, Feldman J, Mirzaa GM, et al (eds). GeneReviews® [Internet], Seattle (WA): University of Washington Nov 4, 2002 [Last Update: Mar 22, 2018].
https://www.ncbi.nlm.nih.gov/books/NBK1139/ (accessed 2024-08-26)

13) Vangala DB, Cauchin E, Balmaña J, et al. Screening and surveillance in hereditary gastrointestinal cancers: Recommendations from the European Society of Digestive Oncology (ESDO) expert discussion at the 20th European Society for Medical Oncology (ESMO)/World Congress on Gastrointestinal Cancer, Barcelona, June 2018. Eur J Cancer. 2018;104:91-103 [PMID: 30342310]

8. Pancreas

Major hereditary cancer syndromes with a high lifetime risk of developing pancreatic cancer (as well as their causative genes) include hereditary breast and ovarian cancer (*BRCA1, BRCA2*), Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*), Peutz-Jeghers syndrome (*STK11*), familial atypical multiple mole-melanoma syndrome (pancreatic cancer-malignant melanoma syndrome) (*CDKN2A*), hereditary pancreatitis (*PRSS1*), and individuals who carry a germline pathogenic variant (GPV) in *ATM* or *PALB2*[1-9]. In addition, hereditary tumor syndromes with a high risk of developing pancreatic and gastrointestinal neuroendocrine tumors include multiple endocrine neoplasia type 1 (*MEN1*) and von Hippel–Lindau disease (*VHL*).

1. Overview

Because MGPT detects GPV in 11–15% of patients with pancreatic cancer[10, 11], the U.S. National Comprehensive Cancer Network (NCCN) guidelines recommend that MGPT be performed on all patients with pancreatic cancer[12], and the 2022 edition of the Japanese Clinical Practice Guidelines for Pancreatic Cancer recommends germline genetic testing for the purpose of assessing the cancer risk in patients and their blood relatives[13]. Currently (as of December 2024), in Japan, only *BRCA1/2* genetic testing can be performed under health insurance coverage for the purpose of selecting treatment with a PARP inhibitor using blood samples from patients with curatively unresectable pancreatic cancer.

Among individuals carrying GPV in genes related to hereditary pancreatic cancer, the lifetime risk of developing pancreatic cancer was reported to be 36% in patients with Peutz-Jeghers syndrome[14], 40–49% in patients with hereditary pancreatitis[15-17], 10–17% in individuals carrying GPV in *CDKN2A*, 5% in patients with hereditary breast and ovarian cancer, and 3.7% in patients with Lynch syndrome[18]. Overseas reports have shown that, among patients with hereditary breast and ovarian cancer, those carrying GPV in *BRCA2* are at high risk of developing pancreatic cancer. In contrast, a recent large-scale case-control study in Japan reported that the risk of developing pancreatic cancer at the age of 85 years was 16% in those carrying GPV in *BRCA1* and 13.7% in those carrying GPV in *BRCA2*, showing a higher risk for both *BRCA1* and *BRCA2* than that reported overseas[19]. Regarding reports of hereditary pancreatitis, the proportion of patients who were confirmed to carry GPV in *PRSS1* varied from 12% to 85%, which included many patients diagnosed based on clinical diagnostic criteria[15-17].

It has been reported that the clinicopathological characteristics of hereditary pancreatic cancer are not greatly different from those of sporadic pancreatic cancer, and it is difficult to differentiate hereditary pancreatic cancer from sporadic pancreatic cancer based only on information about pancreatic cancer.

2. Surveillance methods

According to many domestic and international guidelines, individuals whose lifetime risk of pancreatic cancer is ≥5% or whose relative risk is ≥5 times are considered to be eligible for surveillance[1, 9]. Among patients with Lynch syndrome and GPV carriers of *ATM* or *PALB2*, individuals who have a first (or second) degree relative with pancreatic cancer are eligible for surveillance, and patients with Peutz-Jeghers syndrome, patients with hereditary pancreatitis, and individuals carrying GPV in *CDKN2A* are provided with surveillance, regardless of family history. Regarding imaging tests for surveillance, the use of endoscopic ultrasonography (EUS) and MRI/magnetic resonance cholangiopancreatography (MRCP) is recommended in overseas countries[1, 2, 5, 7]. In Japan, contrast-enhanced CT examination and abdominal ultrasonography (US) are also included based on their versatility and the physical characteristics of the Japanese population[9]. However, EUS, which has a high capacity to visualize small pancreatic masses, and MRI/MRCP, which is superior in visualizing the pancreatic duct system without radiation exposure, are more strongly recommended[9]. Although they can be substituted with contrast-enhanced CT for the observation of other organs, it is desirable to perform thin-section imaging (slice thickness: 1–2 mm) if the risk of pancreatic cancer is high or if abnormal findings have been found in the pancreas. Patients with hereditary pancreatitis often have multiple calcifications and scars in the pancreas, and because they are accompanied by acoustic shadows, observation by EUS (US) is considered difficult, with no consensus achieved on the images to be used for surveillance, even among experts[10]. Also, it is recommended that blood tests, including those for tumor markers (e.g., CEA and CA19-9) and pancreatic exocrine enzymes, be performed along with imaging tests. If changes in images are observed during follow-up or if a mass suggestive of pancreatic cancer is detected, it is recommended to perform pancreatic juice cytodiagnosis using endoscopic retrograde cholangiopancreatography (ERCP)/endoscopic nasopancreatic drainage (ENPD) placement or histological examination using endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), as necessary[9]. Previously, patients undergoing unnecessary pancreatectomy accounted for approximately half of all resection cases, which included unresectable cases that were identified due to advanced cancer[11, 20]. However, a recent prospective study of pancreatic cancer patients in the United States showed that those who received surveillance had a 5-year survival rate of 73.3% and a median survival time of 9.8 years, while those who received no surveillance had a 5-year survival rate of 0% and a median survival time of 1.5 years, showing a favorable outcome of surveillance[3].

For surveillance of pancreatic and gastrointestinal neuroendocrine tumors, see the sections of ***MEN1*** and ***VHL*** in **Chapter 4**.

3. Starting age of surveillance

The recommended starting age of surveillance is 50 years for patients with hereditary breast and ovarian cancer, patients with Lynch syndrome, and GPV carriers of *ATM* or *PALB2* who have a first (or second) degree relative with pancreatic cancer, as well as 30 years for patients with Peutz-Jeghers

syndrome and 40 years for patients with hereditary pancreatitis, regardless of family history of pancreatic cancer. For GPV carriers of *CDKN2A*, it is recommended that surveillance be started 10 years earlier than the age of the pancreatic cancer-affected individual with the earliest onset in the family or at the age of 40 years, whichever is earlier[1, 2, 5, 7].

4. Surveillance intervals

Risk factors for pancreatic cancer include history of smoking and alcohol consumption, history of diabetes and pancreatitis, obesity, and pancreatic findings (e.g., IPMN), in addition to family history and genetic factors[20]. It is recommended that the surveillance interval be determined within the range of 6–12 months depending on the evaluation of various factors, including these risk factors[9]. Overseas, it is recommended that the surveillance be performed at intervals of 12 months if there are no abnormal pancreatic findings. If there are abnormal findings, it is recommended that the surveillance interval be shortened according to the type of the findings[1, 5, 7].

5. Surgical treatment

No studies have reported the use of different criteria or methods of surgical resection between pancreatic cancer with a hereditary risk and sporadic pancreatic cancer. However, hereditary pancreatitis is often accompanied by pain attacks from a young age, and pancreatectomy may be selected for the purpose of pain relief[10].

6. Drug therapy

It has been reported that platinum agents and PARP inhibitors are highly effective in pancreatic cancer patients with breast and ovarian cancer, as in patients with hereditary breast and ovarian cancer[21].

■ References

1) Goggins M, Overbeek KA, Brand R, et al. Management of patients with increased risk for familial pancreatic cancer:updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. Gut. 2020;69(1):7-17. [PMID: 31672839]
2) Daly MB, Pal T, Maxwell KN, et al. NCCN Guidelines® Insights: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2. 2024. J Natl Compr Canc Netw. 2023;21(10):1000-10. [PMID: 37856201]
3) Dbouk M, Katona BW, Brand RE, et al. The Multicenter Cancer of Pancreas Screening Study: Impact on Stage and Survival. J Clin Oncol. 2022;40(28):3257-66. [PMID: 35704792]
4) Canto MI. Screening and surveillance approaches in familial pancreatic cancer. Gastrointest Endosc Clin N Am. 2008;18(3):535-53, x. [PMID: 18674702]
5) Sawhney MS, Calderwood AH, Thosani NC, et al. ASGE guideline on screening for pancreatic cancer

in individuals with genetic susceptibility:summary and recommendations. Gastrointest Endosc. 2022;95(5):817-26. [PMID: 35183358]
6) Casolino R, Paiella S, Azzolina D, et al. Homologous Recombination Deficiency in Pancreatic Cancer: A Systematic Review and Prevalence Meta-Analysis. J Clin Oncol. 2021;39(23):2617-31. [PMID: 34197182]
7) Aslanian HR, Lee JH, Canto MI. AGA Clinical Practice Update on Pancreas Cancer Screening in High-Risk Individuals: Expert Review. Gastroenterology. 2020;159(1):358-62. [PMID: 32416142]
8) Japan Organization of Hereditary Breast and Ovarian Cancer (ed.). Clinical Practice Guidelines for Hereditary Breast and Ovarian Cancer (HBOC), 2024 Edition. Kanehara Publishing Co., Ltd. 2024.
9) Kitano M, Morizane C, Hijioka S, et al. Surveillance for the early diagnosis of familial pancreatic cancer (Expert consensus): Japan Pancreas Society Registry Committee for Familial Pancreatic Cancer and Subcommittee Meeting on Familial Pancreatic Cancer. Suizo. 2020;35(4):322-30.
10) Greenhalf W, Lévy P, Gress T, et al. International consensus guidelines on surveillance for pancreatic cancer in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club. Pancreatology. 2020;20(5):910-8. [PMID: 32624419]
11) Signoretti M, Bruno MJ, Zerboni G, et al. Results of surveillance in individuals at high-risk of pancreatic cancer: A systematic review and meta-analysis. United European Gastroenterol J. 2018;6(4):489-99. [PMID: 29881603]
12) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment:Breast, Ovarian and Pancreatic. Version 3. 2024. (accessed 2024-08-26)
13) Revision Committee of Clinical Practice Guidelines for Pancreatic Cancer, Japan Pancreas Society (ed.). Clinical Practice Guidelines for Pancreatic Cancer, 2022 Edition. Kanehara Publishing Co., Ltd.
https://www.suizou.org/pdf/pancreatic_cancer_cpg-2022.pdf
14) Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology. 2000;119(6):1447-53. [PMID: 11113065]
15) Lowenfels AB, Maisonneuve P, DiMagno EP, et al. Hereditary pancreatitis and the risk of ancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst. 1997;89(6):442-6. [PMID: 9091646]
16) Howes N, Lerch MM, Greenhalf W, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin Gastroenterol Hepatol. 2004;2(3):252-61. [PMID: 15017610]
17) Rebours V, Boutron-Ruault MC, Schnee M, et al. Risk of pancreatic adenocarcinoma in patients with hereditary pancreatitis:a national exhaustive series. Am J Gastroenterol. 2008;103(1):111-9. [PMID:

18184119]
18) Hijioka S, Morizane C, Saito Y. Surveillance for the Detection of Early-Stage Pancreatic Cancer in Individuals with Risk for Familial Pancreatic Cancer and Hereditary Pancreatic Cancer Syndrome: Global Trends. Gastroenterological Endoscopy. 2022;64(5):1089-98.
19) Momozawa Y, Sasai R, Usui Y, et al. Expansion of Cancer Risk Profile for BRCA1 and BRCA2 Pathogenic Variants. JAMA Oncol. 2022;8(6):871-8. [PMID: 35420638]
20) Paiella S, Salvia R, De Pastena M, et al. Screening/surveillance programs for pancreatic cancer in familial high-risk individuals: A systematic review and proportion meta-analysis of screening results. Pancreatology. 2018;18(4):420-8. [PMID: 29709409]
21) Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. N Engl J Med. 2019;381(4):317-27. [PMID: 31157963]

9. Biliary tract

Hereditary cancer syndromes with a high lifetime risk of developing biliary tract cancer (as well as their causative genes) include hereditary breast and ovarian cancer (*BRCA1, BRCA2*), Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*), familial adenomatous polyposis (familial polyposis coli) (*APC*), Peutz-Jeghers syndrome (*STK11*), and individuals who carry a germline pathogenic variant (GPV) in *PALB2*.

1. Overview

It has been reported that hereditary biliary tract cancer occurs in 5.5–16.0% of biliary tract cancer patients with a family history of biliary tract cancer[1, 2]. A cancer-specific panel targeting 27 genes (cancer-specific MGPT) was performed on 1,292 Japanese patients with biliary tract cancer, and it detected GPV at a frequency of 5.5%, with variant genes including *BRCA1/2* and other homologous recombination-related genes, mismatch repair genes, and *APC*. In hereditary breast and ovarian cancer patients with biliary tract cancer, the proportion of those carrying GPV in *BRCA2* is larger than the proportion of those carrying GPV in *BRCA1*[1, 2]. In overseas countries, patients with Lynch syndrome carrying GPV in *MLH1* are at high risk of developing biliary tract cancer[3], but in Japan, the proportion of those carrying GPV in *MSH6* is high among patients with biliary tract cancer[1, 2]. A large proportion of patients with familial adenomatous polyposis develop duodenal papillary carcinomas among biliary tract cancers.

2. Surveillance methods

There is insufficient evidence to recommend biliary surveillance for individuals carrying GPV in genes related to hereditary biliary tract cancer. However, the presence or absence of abnormal findings in the biliary tract should be examined to the possible extent when performing pancreatic surveillance (abdominal MRI examination), duodenal surveillance (upper gastrointestinal endoscopy), and other abdominal surveillances (abdominal ultrasonography). Also, in patients with familial adenomatous polyposis, duodenal papillae should be observed by upper gastrointestinal endoscopy at the time of colectomy or at the age of 20–25 years; treatment should be considered if a papillary tumor with a size of ≥1 cm is found, if biopsy shows histological findings such as advanced atypical adenoma and tubulovillous adenoma, or if there are findings caused by obstruction of the pancreaticobiliary duct including liver dysfunction and pancreatitis. Also, endoscopic papillectomy at a specialized facility should be considered first[4, 5].

3. Starting age of surveillance and its intervals

See **Chapter 4** for the recommended starting age and intervals of pancreatic, duodenal, and abdominal surveillances for each cancer predisposition disease.

4. Treatment

In recent years, there have been some reports on the efficacy of platinum agents and PARP inhibitors for *BRCA1/2* pathogenic variant-positive biliary tract cancer, as well as immune checkpoint inhibitors for MSI-High biliary tract cancer. However, evidence remains insufficient for patients with hereditary tumors. Surgical and pharmacological treatment of hereditary biliary tract cancer should be performed in the same manner as that of sporadic biliary tract cancer.

■ References

1) Maynard H, Stadler ZK, Berger MF, et al. Germline alterations in patients with biliary tract cancers: A spectrum of significant and previously underappreciated findings. Cancer. 2020;126 (9):1995-2002. [PMID: 32012241]
2) Okawa Y, Iwasaki Y, Johnson TA, et al. Hereditary cancer variants and homologous recombination deficiency in biliary tract cancer. J Hepatol. 2023;78(2):333-42. [PMID: 36243179]
3) Møller P, Seppälä TT, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. Gut. 2018; 67(7):1306-16. [PMID: 28754778]
4) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 2, 2024. (accessed 2024-10-1)
5) Japanese Society for Cancer of the Colon and Rectum (ed.). Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition. Kanehara Publishing Co., Ltd.

10. Large intestine

Hereditary cancer syndromes with a high lifetime risk of developing colorectal cancer, as well as their causative genes, can be broadly divided into those with and without polyposis coli. Furthermore, patients with polyposis coli can be divided into those with adenomatous, hamartomatous, and serrated polyposes depending on the histological type. Adenomatous polyposes include familial adenomatous polyposis (familial polyposis coli) (*APC*), *MUTYH*-associated polyposis (*MUTYH*), and polymerase proofreading-associated polyposis (*POLE, POLD1*), but they can also be caused by *AXIN2*, *MLH3*, *MSH3*, or *NTHL1*. Hereditary tumor syndromes with hamartomatous polyposis include Peutz-Jeghers syndrome (*STK11*), juvenile polyposis syndrome (*SMAD4, BMPR1A*), and Cowden syndrome/*PTEN* hamartoma tumor syndrome (*PTEN*). It has been reported that some patients with serrated polyposis carry GPV in *RNF43* or *GREM1*, but environmental factors are also likely be involved. Hereditary tumor syndromes without polyposis coli include Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*), Li-Fraumeni syndrome (*TP53*), and Birt-Hogg-Dubé (BHD) syndrome *(FLCN)*. However, patients with constitutional mismatch repair deficiency (CMMRD) syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*) develop adenomatous polyposis from childhood. Additionally, it has been reported that individuals who carry GPV in *MUTYH* in the heterozygous state (one allele) have a slightly increased risk of developing colorectal cancer. It has also been reported that individuals who carry GPV in *BLM*, *CHEK2*, *GALNT12*, or *RPS20* have an increased risk of developing colorectal cancer.

1. Overview

Diagnosis of hereditary colorectal cancer involves three steps: risk assessment based on clinical information (Step 1), histopathologic/molecular pathological assessment (Step 2), and genetic testing (Step 3). If polyposis coli is found in Step 1, a biopsy should be performed to examine the histological type. If the patient has a small number of polyps, microsatellite instability (MSI) testing or mismatch repair protein immunohistochemistry (MMRIHC) testing is performed. Even after following the above steps, there are still several diseases that should be differentiated in the diagnosis of hereditary colorectal cancer, and thus, it is recommended that genetic testing by MGPT be performed for patients suspected of having hereditary colorectal cancer. In addition, even if Lynch syndrome is suspected in Steps 1 and 2, diagnosis by genetic testing is necessary since the patient may have Lynch-like syndrome, which is mainly caused by a somatic variant of MMR genes at both alleles. Also, in patients with Lynch syndrome, the lifetime risk of developing Lynch syndrome-related tumors, including colorectal cancer, varies depending on the causative gene. Therefore, the causative gene needs to be identified in order to provide appropriate surveillance.

2. Surveillance methods

For individuals carrying GPV in genes related to hereditary colorectal cancer, colon surveillance is performed with colonoscopy. With recent advances in endoscopic devices, the usefulness of magnified observation and narrow band imaging has been reported, but no studies have demonstrated the usefulness of colonoscopy combined with these observation methods in colon surveillance of individuals carrying GPV in genes related to hereditary colorectal cancer. In colonoscopy of individuals carrying GPV in genes related to hereditary colorectal cancer, it is desirable to remove all polyps with a size of ≥5 mm[1]. No studies have shown that endoscopic removal of polyps detected during colonoscopy prevents the development of colorectal cancer in those carrying GPV in genes related to hereditary colorectal cancer. However, it was reported that intensive downstaging polypectomy (IDP) may be a useful means for preventing colorectal cancer without total colorectomy in patients with familial adenomatous polyposis, excluding the dense form, and IDP was covered by insurance in 2022[2]. However, caution is needed when performing IDP since the necessity of colorectal surgery is unclear in patients receiving IDP for a long period of time. Patients with hamartomatous polyposis, including those with Peutz-Jeghers syndrome, juvenile polyposis syndrome, or Cowden syndrome/*PTEN* hamartoma tumor syndrome, may develop polyps and cancer in the jejunum and ileum, and it is recommended that periodic surveillance endoscopy or imaging examination be performed, especially for patients with Peutz-Jeghers syndrome. The occurrence of polyps and cancer in the jejunum and ileum has also been reported in patients with familial adenomatous polyposis. However, the cumulative occurrence risk of small intestinal cancer was reported to be <1%, and periodic surveillance endoscopy is not recommended. In patients with Lynch syndrome, colonoscopy surveillance has been shown to reduce the mortality rate from colorectal cancer by 60–72%[3], and thus, colonoscopy is strongly recommended.

3. Starting age of surveillance

For individuals carrying GPV in genes related to hereditary colorectal cancer, the starting age of colon surveillance has been proposed according to the risk of developing colorectal cancer, as well as symptoms due to polyps.

The starting age of colon surveillance for patients with familial adenomatous polyposis varies depending on adenoma density. In patients with classic familial adenomatous polyposis (FAP), colon surveillance should be started after the age of 10 years, or in the late teens (18–20 years) if the patient has attenuated FAP (AFAP) with a small number of adenomas (<100). Also, it is recommended that colon surveillance be started in the teenage years even for patients with *MUTYH*-associated polyposis, in whom there are often fewer than 100 colorectal polyps.

For patients with Peutz-Jeghers syndrome, who are known to develop intussusception and intestinal obstruction at a relatively young age due to polyps, colonoscopy is recommended at the age of 8 years, and surveillance of the jejunum and ileum with MR enterography or small bowel capsule endoscopy is

recommended from the age of 8 years. For patients with juvenile polyposis syndrome, who also develop hamartomatous polyposis, it is recommended that colon surveillance be started in the teenage years.

For patients with Lynch syndrome, the recommended starting age of colon surveillance varies depending on the causative gene. It is recommended that colon surveillance be started at the age of 20–25 years for those having *MLH1* or *MSH2/EPCAM* as the causative gene and 30–35 years for those having *MSH6* or *PMS2* as the causative gene. However, consideration should also be given to starting colon surveillance 2–5 years earlier than the age of the youngest affected member of the family. For patients with Li-Fraumeni syndrome, it is recommended that surveillance colonoscopy be started at the age of 25 years.

See **Chapter 4** for responses specific to other genes.

4. Surveillance intervals

For individuals carrying GPV in genes related to hereditary colorectal cancer, colon surveillance is generally performed at intervals of 1–2 (3) years, but the intervals of colon surveillance should be determined based on the presence and density of polyps. See **Chapter 4** for gene-specific responses.

Even if there are no recommended optimal intervals of colon surveillance, it should be performed at intervals of 1–2 (3) years in individuals carrying GPV in genes related to hereditary colorectal cancer, considering the presence and density of polyps.

5. Chemoprevention

In patients with familial adenomatous polyposis, the administration of sulindac, a nonsteroidal anti-inflammatory drug (NSAID), has been shown to suppress the increase in the number and size of colorectal adenomas[4]. However, there has been no evidence that it reduces the risk of developing colorectal cancer[5], and the growth of adenomas after the discontinuation of sulindac, as well as mucosal damage due to its long-term administration, has also been pointed out. Although the administration of celecoxib, a selective COX-2 inhibitor, has been shown to reduce the number and size of colorectal adenomas[6], the increased risk of cardiovascular events is an issue[7]. The administration of low-dose aspirin (100 mg/day for 8 months) has been shown to significantly suppress polyp growth, but the effect of its long-term administration is unknown[8]. In patients with Lynch syndrome, a study has reported that the administration of aspirin (600 mg/day) for ≥2 years reduces the occurrence of colorectal cancer, but the data must be interpreted with caution due to the large number of subjects who dropped out during the study period[9]. In addition, because aspirin is administered in high doses, there is a risk of gastrointestinal disturbance and bleeding.

6. Surgical treatment

Prophylactic colorectal surgery is considered for patients with familial adenomatous polyposis if management with endoscopic treatment is no longer feasible or if progression of adenoma density is observed[10]. Total colorectomy is the standard surgical procedure for patients with ≥100 adenomas or ≥20 rectal adenomas, but total colectomy is also an option for patients with a small number of adenomas. Partial resection may be selected for patients who have developed incurable colorectal cancer.

In patients with Lynch syndrome, it has been reported that extensive surgery reduces the risk of developing metachronous colorectal cancer, but a favorable prognosis has been reported with the same extent of resection as that for sporadic colorectal cancer.

7. Drug therapy

In patients with hereditary colorectal cancer, drug therapy for colorectal cancer should be performed in the same manner as that for sporadic colorectal cancer. Also, most colorectal cancers occurring in patients with Lynch syndrome are known to exhibit high-frequency microsatellite instability (MSI-High), and the administration of immune checkpoint inhibitors should be considered once the cancer is confirmed to exhibit MSI-High[11].

■ References

1) Yen T, Stanich PP, Axell L, et al. APC-Associated Polyposis Conditions. Adam MP, Feldman J, Mirzaa GM, et al (eds). GeneReviews® [Internet], Seattle (WA): University of Washington Dec 18, 1998[Last update: May 12, 2022] https://www.ncbi.nlm.nih.gov/books/NBK1345/ (accessed 2024-08-26)

2) Ishikawa H, Yamada M, Sato Y, et al. Intensive endoscopic resection for downstaging of polyp burden in patients with familial adenomatous polyposis (J-FAPP Study Ⅲ): a multicenter prospective interventional study. Endoscopy. 2023;55(4):344-52. [PMID: 36216266]

3) Järvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology. 2000;118 (5):829-34. [PMID: 10784581]

4) Giardiello FM, Hamilton SR, Krush AJ, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med. 1993;328(18):1313-6. [PMID: 8385741]

5) Giardiello FM, Yang VW, Hylind LM, et al. Primary chemoprevention of familial adenomatous polyposis with sulindac. N Engl J Med. 2002;346(14):1054-9. [PMID: 11932472]

6) Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med. 2000;342(26):1946-52. [PMID: 10874062]

7) Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med. 2005;352(11):1071-80. [PMID: 15713944]

8) Ishikawa H, Mutoh M, Sato Y, et al. Chemoprevention with low-dose aspirin, mesalazine, or both in patients with familial adenomatous polyposis without previous colectomy (J-FAPP Study IV): a multicentre, double-blind, randomised, two-by-two factorial design trial. Lancet Gastroenterol Hepatol. 2021;6(6):474-81. [PMID: 33812492]

9) Burn J, Sheth H, Elliott F, et al. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. Lancet. 2020;395(10240):1855-63. [PMID: 32534647]

10) Lynch PM, Morris JS, Wen S, et al. A proposed staging system and stage-specific interventions for familial adenomatous polyposis. Gastrointest Endosc. 2016;84(1):115-25. e4. [PMID: 26769407]

11) André T, Shiu KK, Kim TW, et al. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. N Engl J Med. 2020;383(23):2207-18. [PMID: 33264544]

11. Kidneys

Hereditary cancer syndromes with a high lifetime risk of developing renal cancer (as well as their causative genes) include von Hippel–Lindau disease (*VHL*), Birt-Hogg-Dubé syndrome (*FLCN*), hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome (*FH* tumor predisposition syndrome) (*FH*), hereditary papillary renal cell carcinoma (*MET*), hereditary pheochromocytoma and paraganglioma (PPGL) syndrome (*SDHB, SDHC, SDHD*), Cowden syndrome/*PTEN* hamartoma tumor syndrome (*PTEN*), tuberous sclerosis (*TSC1, TSC2*), Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*), *WT1*-related Wilms tumor (Wilms tumor predisposition) (*WT1*), and individuals who carry a germline pathogenic variant (GPV) in *BAP1*, *CHEK2*, or *PBRM1*. Patients with *DICER1* syndrome (*DICER1* tumor predisposition) (*DICER1*) carry a risk of developing cystic nephroma.

1. Overview

Hereditary renal tumors have different tumor characteristics depending on the causative gene, and for each, there are different methods of follow-up and treatment[1]. It is important to identify family lines with hereditary renal tumors prior to tumor development and to guide GPV carriers to surveillance at an appropriate time.

2. Surveillance methods

The timing to start renal surveillance for GPV carriers varies depending on the hereditary renal tumor, and renal surveillance should be started before the age of onset of the youngest reported case of each hereditary tumor. Regarding the method of surveillance, imaging tests, such as abdominal ultrasonography, abdominal CT examination, and abdominal MRI examination, are performed every 6 months to 3 years, but the intervals between tests should be determined according to the tumor characteristics of the hereditary renal tumor that may occur[1].

3. Surgical treatment

Hereditary renal tumors have different tumor characteristics depending on the causative gene, and they are broadly divided into those that can be treated with active surveillance and those that require immediate surgery. Hereditary renal tumors that can be treated with active surveillance occur in patients with von Hippel–Lindau (VHL) disease, Birt-Hogg-Dubé (BHD) syndrome, hereditary papillary renal cell carcinoma (HPRC), *BAP1* tumor predisposition syndrome, and other diseases. These tumors occur bilaterally and metachronously. Thus, in the United States, surgical treatment is considered when the diameter of the largest tumor reaches 3 cm. In Japan, however, surgical treatment is considered when the diameter reaches 2 cm, taking into account the difference in body size between Japanese and

Westerners[2, 3]. It has been reported that VHL-related renal cancer, BHD-related renal cancer, HPRC, and *BAP1*-related renal cancer grow by 0.37 cm, 0.1 cm, 0.15 cm, and 0.6 cm per year, respectively, and early intervention with close surveillance should be considered for *BAP1*-related renal cancer since it grows at a relatively rapid rate[3]. Hereditary renal tumors that should be considered for immediate surgery occur in patients with HLRCC syndrome and hereditary PPGL syndrome, which may involve lymph node metastasis and are highly malignant even though they are small in diameter[2].

Regarding the surgical method, enucleation with minimal resection margins is performed for patients with VHL-related renal cancer, BHD-related renal cancer, or HPRC, and nephrectomy should be avoided. In patients with *BAP1*-related renal cancer, HLRCC, or PPGL-related renal cancer, large resection margins should be secured, and nephrectomy is performed if resection margins cannot be secured. In patients with HLRCC, postoperative local recurrence often becomes an issue, and laparotomy and wound lavage with large volumes of saline solution are performed in combination, as necessary[2, 3]. Hereditary renal tumors other than those described above should, in principle, be treated in the same manner as that for isolated cases, but it should be noted that information on methods of follow-up and treatment is updated daily, especially for hereditary renal tumors with a low frequency.

4. Drug therapy

Metastatic patients are, in principle, treated with insurance-covered renal cancer drugs, and it is important to understand their effect on the function of each causative gene[2]. Currently, the pathways targeted by insurance-covered renal cancer drug therapy are the hypoxic response, the mTOR pathway, and immune checkpoints; hypoxic response-related genes include *VHL*, *FH*, *SDHB*, *SDHC*, and *SDHD*, and mTOR pathway-related genes include *FLCN*, *PTEN*, *TSC1*, and *TSC2*[2]. In addition, MMR genes, such as *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*, correlate with the efficacy of immune checkpoint inhibitors, as they are associated with tumor mutation burden (TMB). The methods need to be further developed to predict and enhance the efficacy of renal cancer drug therapy based on functional analysis of renal cancer-related genes.

■ References

1) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Kidney Cancer Version 3. 2024.
https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf
2) Hasumi J, Hamanoue H. All about surveillance therapy for urologic tumors.④ Hereditary renal cancer. Urological Surgery. 2023;36 (in Japanese)11) : 1196-202.
3) Ball MW, An JY, Gomella PT, et al. Growth Rates of Genetically Defined Renal Tumors: Implications for Active Surveillance and Intervention. J Clin Oncol. 2020;38(11):1146-53. [PMID: 32083993].

12. Adrenal glands

Hereditary cancer syndromes with a high lifetime risk of developing pheochromocytoma and paraganglioma (PPGL) include multiple endocrine neoplasia type 2 (*RET*), von Hippel–Lindau disease (*VHL*), and hereditary PPGL syndrome (*SDHA, SDHAF2, SDHB, SDHC, SDHD, MAX, TMEM127*). Also, hereditary tumor syndromes with a high lifetime risk of developing adrenocortical carcinomas include Li-Fraumeni syndrome (*TP53*). In addition, hereditary cancer syndromes with a high lifetime risk of developing benign adrenocortical tumors include multiple endocrine neoplasia type 1 (*MEN1*).

1. Overview

Currently, there are more than 10 known causative genes of PPGL, which arises from paraganglioma in the adrenal medulla or throughout the body, and 30–40% of all cases of PPGL are considered to be hereditary[1]. The penetration rate, site of frequent occurrence, common age of onset, and malignant grade vary depending on the causative gene. Many causative genes cause only PPGL, but *RET* and *VHL* cause PPGL (mostly adrenal pheochromocytoma) as a partial disease of multiple endocrine neoplasia type 2 (MEN2) and von Hippel–Lindau disease, respectively.

Many patients with adrenocortical carcinomas associated with Li-Fraumeni syndrome are diagnosed before the age of 5 years[2]. Approximately 70% of adrenocortical carcinomas that develop before the age of 20 years are due to Li-Fraumeni syndrome[3]. Approximately 20% of patients with multiple endocrine neoplasia type 1 (MEN1) develop adrenocortical tumors, but many of them receive only follow-up since they are nonfunctioning benign tumors that show no growth tendency.

2. Surveillance methods

Surveillance of pheochromocytoma mainly involves catecholamine quantification and imaging diagnosis. Previously, catecholamine levels were measured by plasma adrenaline/noradrenaline or 24-hour urinary metanephrine/normetanephrine fractions. However, measurement of plasma free metanephrine/normetanephrine, which is simpler and has higher sensitivity and specificity, has recently been covered by insurance (however, it has been stated that it is calculated only once if differential diagnosis of pheochromocytoma has been made). Imaging diagnosis is performed mainly with MRI.

In patients with Li-Fraumeni syndrome, abdominal ultrasonography and measurement of adrenocortical hormones are performed to diagnose adrenocortical carcinomas, which can also be confirmed by surveillance with whole-body MRI. CT examination should be avoided due to high radiosensitivity.

In patients with MEN1, abdominal CT/MRI examination is performed for the surveillance of pancreatic and gastrointestinal neuroendocrine tumors, during which the adrenal glands can also be evaluated.

3. Starting age of surveillance

The starting age of surveillance for PPGL varies depending on the causative gene, but it is generally started in childhood. In patients with MEN2, the penetration rate of PPGL varies depending on the codon of GPV[4], and thus, surveillance for low-risk GPV carriers is started later than that for high-risk GPV carriers.

Adrenal surveillance for patients with Li-Fraumeni syndrome should be started from birth.

4. Surveillance intervals

Surveillance for patients with PPGL is generally performed at intervals of 1–2 years. Surveillance of adrenocortical carcinomas in patients with Li-Fraumeni syndrome should be performed at intervals of 3–4 months, at least during childhood.

See **Chapter 4** for gene-specific responses.

5. Surgical treatment

All patients with PPGL are indicated for surgery. Tumors occurring in the adrenal medulla are treated with laparoscopic tumor resection. Treatment of patients with tumors occurring in the carotid arteries should be determined individually based on the risk of complications, such as nerve damage caused by surgery, and the risk of malignancy due to the causative gene.

Adrenocortical carcinomas in patients with Li-Fraumeni syndrome are treated with conventional surgery. Adrenocortical tumors in patients with MEN1 are usually managed with follow-up only, since they are nonfunctioning and have little growth tendency.

6. Drug therapy

Patients with catecholamine-producing pheochromocytomas require sufficient preoperative administration of α-blockers or $\alpha\beta$-blockers to increase circulating plasma volume.

For unresectable or metastatic pheochromocytoma, the use of the tyrosine hydroxylase inhibitor metyrosine is covered by insurance as a drug to improve catecholamine hypersecretion. As needed, α-blockers or $\alpha\beta$-blockers are used in combination to reduce symptoms caused by excess catecholamines.

Patients with unresectable or metastatic adrenocortical carcinomas are administered mitotane. Trilostane, metyrapone, and osilodrostat, in addition to mitotane, are listed as insurance-covered oral drugs for the suppression of cortisol biosynthesis.

■ References

1) Neumann HPH, Young WF Jr, Eng C. Pheochromocytoma and Paraganglioma. n Engl J Med. 2019; 381(6):552-65.[PMID: 31390501]
2) Mai PL, Best AF, Peters JA, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni Cancer. 2016;122(23):3673-81.[PMID: 27496084].
3) Zhang J, Walsh MF, Wu G, et al. Germline Mutations in Predisposition Genes in Pediatric Cancer. N Engl J Med. 2015; 373(24):2336-46.[PMID: 26580448].
4) Imai T, Uchino S, Okamoto T, et al. High penetrance of pheochromocytoma in multiple endocrine neoplasia 2 caused by germ line RET codon 634 mutation in Eur J Endocrinol. 2013;168(5):683-7. [PMID: 23416954].

13. Upper urinary tract

Hereditary cancer syndromes with a high lifetime risk of developing upper urothelial tumors include Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*).

1. Overview

In the analysis of upper urothelial tumors, including isolated cases, deletion of MSH2 or MSH6 protein was found in 5.0–11.3% of cases, and GPV in mismatch repair (MMR) genes was found in 5% of cases[1-3]. In Japan, a study examined 27 genes related to hereditary tumor syndromes, and GPV in MMR genes was detected in 3 (1.44%) of 208 patients with upper urothelial tumors[4].

Patients with Lynch syndrome have a high lifetime risk of developing tumors in the upper urothelium, which consists of the renal pelvis and ureter[5, 6]. Particularly in patients with Lynch syndrome who carry GPV in *MSH2* or *EPCAM*, the cumulative risk of developing upper urothelial tumors by the age of 80 years was found to be 2.2–28%, indicating a higher risk of developing upper urothelial cancer than those who carry GPV in other causative genes[7].

2. Surveillance methods

Urinalysis and urine cytology should be performed annually starting at the age of 30-35 years[6, 7].

3. Treatment methods

Upper urothelial cancer occurring in patients with hereditary tumor syndromes should be treated in the same manner as that for isolated cases (sporadic cases). In other words, surgical indication is determined based on imaging tests and clinical disease stage, and if it is determined to be curable, surgical treatment should be performed, such as total nephroureterectomy, partial ureterectomy, and ureteroscopic laser ablation. On the other hand, chemotherapy is performed if radical resection is not possible or if distant metastasis is detected.

■ References

1) Urakami S, Inoshita N, Oka S, et al. Clinicopathological characteristics of patients with upper urinary tract urothelial cancer with loss of immunohistochemical expression of the DNA mismatch repair proteins in universal screening. Int J Urol. 2018; 25(2): 151-6.[PMID: 29164703].
2) Harper HL, McKenney JK, Heald B, et al. Upper tract urothelial carcinomas: frequency of association with mismatch repair protein loss and lynch syndrome. mod Pathol. 2017; 30(1):146-56.[PMID: 27713421].
3) Metcalfe MJ, Petros FG, Rao P, et al. Universal Point of Care Testing for Lynch Syndrome in Patients

with Upper Tract Urothelial Carcinoma. J Urol. 2018; 199(1):60-5 [. PMID: 28797715]
4) Sekine Y, Iwasaki Y, Hakozaki N, et al. Prevalence and risk estimation of cancer-predisposing genes for upper urinary tract urothelial carcinoma in Jpn J Clin Oncol. 2022;52(12):1441-5. [PMID: 36093724].
5) Hasumi H, Yao M. Lynch Syndrome-Associated Urological Malignancies. In Tomita N (ed) Lynch Syndrome. Singapore, Springer, 2020, 79-83.
6) Colorectal Cancer Study Group, ed. Hereditary Colorectal Cancer Clinical Practice Guideline 2024, Kanehara Shuppan, 2024.
(7) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1, 2024. (Accessed 2024-08-26)

14. Prostate gland

Hereditary cancer syndromes with a high lifetime risk of developing prostate cancer (as well as their causative genes) include hereditary breast and ovarian cancer (*BRCA1, BRCA2*), Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*), and individuals who carry a germline pathogenic variant (GPV) in *HOXB13*. In addition, the detection of GPV in *ATM, ATR, BRIP1, CHEK2, FAM175A, GEN1, MRE11A, NBN, PALB2, RAD51C,* and *RAD51D* has been reported in patients with metastatic prostate cancer[1].

1. Overview

Patients with hereditary prostate cancer are estimated to account for 12–17% of patients with metastatic prostate cancer, and the most common causative cancer susceptibility gene is *BRCA2*, followed by *BRCA1*[1]. A study in Japan examined germline variants in 7,636 patients with prostate cancer, including those with non-metastatic cancer, and found significant associations with *BRCA2, HOXB13,* and *ATM*, with the three genes having a total prevalence of 2.4%[2]. Also, it has been reported that prostate cancer with GPV in *BRCA2* has a higher degree of progression and malignancy at diagnosis[3, 4].

The National Comprehensive Cancer Network (NCCN) guidelines recommend that MGPT be performed in prostate cancer patients with metastatic prostate cancer, high-risk prostate cancer, or a family history of hereditary breast and ovarian cancer-related tumors[5]. In Japan, *BRCA1/2* genetic testing can be performed under insurance-covered medical care for the purpose of selecting treatment with a PARP inhibitor using blood samples from patients with metastatic castration-resistant prostate cancer.

In particular, p.G84E and p.X285K in *HOXB13* have been reported to be associated with the risk of developing hereditary prostate cancer[6, 7]. Interestingly, p.G132E accounts for the majority of GPVs in *HOXB13* among the Japanese population, which greatly differs from the finding in Western cohorts[2].

2. Surveillance methods

In the general population, prostate surveillance, including prostate-specific antigen (PSA) measurement, is often started at the age of 50 years. However, the cumulative incidence rate of prostate cancer up to the age of 75 years is 27% in men carrying GPV in *BRCA2* and 21% in men carrying GPV in *BRCA1*, indicating a high frequency of its early onset. For this reason, it is recommended that testing be started at the age of 40 years or 10 years earlier than the age of onset of the youngest prostate cancer patient in the family[3]. Additionally, the recommended cutoff value for PSA surveillance is 3.0 ng/mL. In patients with Lynch syndrome, the cutoff value is determined according to family history and other

factors[8, 9]. Even for men carrying GPV in other genes, it is recommended that prostate surveillance be started at the age of 40 years or 10 years earlier than the age of onset of the youngest prostate cancer patient in the family[3].

3. Treatment methods

The BRACAnalysis® Diagnostic System can be used in patients with metastatic castration-resistant prostate cancer for the purpose of selecting treatment with a PARP inhibitor, and olaparib can be administered if GPV is detected in *BRCA1* or *BRCA2* (as of August 31, 2024)[10]. In addition, FoundationOne® CDx Cancer Genome Profile or FoundationOne® Liquid CDx Cancer Genome Profile can be used as CGP in patients with metastatic prostate cancer who have completed standard treatment (including those who are expected to complete treatment), and olaparib or talazoparib can be administered if a pathogenic variant is detected in *BRCA1* or *BRCA2* (as of August 31, 2024). However, PARP inhibitors can be used based on the recommendations of the expert panel if the CGP has not been approved as companion diagnostics for PARP inhibitors.

The drug therapy for patients with prostate cancer, except for those with hereditary breast and ovarian cancer, is performed in the same manner as that for patients with isolated prostate cancer.

■ References

1) Pritchard CC, Mateo J, Walsh MF, et al. Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer. N Engl J Med. 2016;375(5):443-53. [PMID: 27433846]
2) Momozawa Y, Iwasaki Y, Hirata M, Liu X, et al. Germline Pathogenic Variants in 7636 Japanese Patients With Prostate Cancer and 12 366 Controls. J Natl Cancer Inst. 2020;112(4):369-76. [PMID: 31214711]
3) Giri VN, Knudsen KE, Kelly WK, et al. Implementation of Germline Testing for Prostate Cancer: Philadelphia Prostate Cancer Consensus Conference 2019. J Clin Oncol. 2020;38(24):2798-811. [PMID: 32516092]
4) Kimura H, Mizuno K, Shiota M, et al. Prognostic significance of pathogenic variants in BRCA1, BRCA2, ATM and PALB2 genes in men undergoing hormonal therapy for advanced prostate cancer. Br J Cancer. 2022;127(9):1680-90. [PMID: 35986085]
5) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic. Version 3. 2024. (accessed 2024-08-26)
6) Ewing CM, Ray AM, Lange EM, et al. Germline mutations in HOXB13 and prostate-cancer risk. N Engl J Med. 2012;366(2):141-9. [PMID: 22236224]
7) Darst BF, Hughley R, Pfennig A, et al. A Rare Germline HOXB13 Variant Contributes to Risk of Prostate Cancer in Men of African Ancestry. Eur Urol. 2022;81(5):458-62. [PMID: 35031163]

8) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024. (accessed 2024-08-26)
9) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer Early Detection. Version 2. 2024.
10) Japanese Urological Association. Considerations for Performing Companion Diagnostics for PARP Inhibitors in Prostate Cancer (Views Report). March 2024. 2024.
https://www.urol.or.jp/lib/files/other/guideline/kenkai_parp_v6.pdf (reference 2024-08-26)

15. Cervix

Major hereditary cancer syndromes with a high lifetime risk of developing cervical cancer include Peutz-Jeghers syndrome (*STK11*) and *DICER1* syndrome (*DICER1* tumor predisposition) (*DICER1*).

1. Overview

Cervical cancer is mainly caused by infection with human papillomavirus (HPV), but patients with Peutz-Jeghers syndrome are at high risk of developing cervical cancer, regardless of the presence or absence of HPV infection. Regarding the histological type, they may develop HPV-independent gastric-type adenocarcinomas or minimal deviation adenocarcinomas (a subtype of HPV-independent gastric-type adenocarcinomas), unlike squamous cell carcinomas, which account for the majority of cervical cancers. The cumulative risk of cervical cancer in patients with Peutz-Jeghers syndrome was reported to be 10–23%[1]. Since it occurs at a relatively young age, appropriate surveillance is necessary from a young age. Patients with *DICER1* syndrome may develop embryonal-type rhabdomyosarcoma in the cervix.

2. Surveillance

In patients with Peutz-Jeghers syndrome, cervical surveillance is performed with minimally invasive cervical cytology[2-6]. However, they have low sensitivity to cytology, unlike those with conventional HPV-associated cervical cancer; a study reported that 50% of patients with Peutz-Jeghers syndrome were judged to be normal, including those with lobular endocervical glandular hyperplasia (LEGH), which is considered to be the site for the development of gastric-type adenocarcinomas, or gastric-type adenocarcinomas[7]. Therefore, cervical biopsy, transvaginal ultrasonography, and contrast-enhanced pelvic MRI should be considered if necessary. However, even if cervical biopsy is performed, the diagnosis of LEGH and gastric-type adenocarcinomas is challenging.

In patients with Peutz-Jeghers syndrome, the median onset age of cervical cancer is 30–40 years. Thus, surveillance should be performed annually starting at the age of 25 years[2-5], but some guidelines recommend that surveillance be started even earlier (at the age of 18–20 years)[3, 4, 6]. Cervical cytology alone in countermeasure-type screening is insufficient due to the low sensitivity to cervical cytology.

3. Prevention

Vaccines are effective in preventing HPV infection, which is a common cause of cervical cancer. However, since cervical cancer in patients with Peutz-Jeghers syndrome is not dependent on HPV, there are no known drugs effective in preventing the development of cervical cancer.

4. Surgical treatment

There is currently insufficient evidence for total hysterectomy aimed at reducing the risk of cervical cancer associated with Peutz-Jeghers syndrome. However, total hysterectomy can be considered when the patient no longer has the desire to have children[8]. In patients with Peutz-Jeghers syndrome, surgical treatment for cervical cancer is performed in the same manner as that for sporadic cervical cancer.

■ References

1) van Lier MG, Wagner A, Mathus-Vliegen EM, et al. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenterol. 2010;105(6): 1258-64; author reply 1265. [PMID: 20051941]
2) Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223-62; quiz 263. [PMID: 25645574]
3) Beggs AD, Latchford AR, Vasen HF, et al. Peutz-Jeghers syndrome:a systematic review and recommendations for management. Gut. 2010;59(7):975-86. [PMID: 20581245]
4) Provenzale D, Gupta S, Ahnen DJ, et al. NCCN Guidelines Insights: Colorectal Cancer Screening, Version 1. 2018. J Natl Compr Canc Netw. 2018;16(8):939-49. [PMID: 30099370]
5) McGarrity TJ, Amos CI, Baker MJ. Peutz-Jeghers Syndrome. Adam MP, Feldman J, Mirzaa GM, et al (eds). GeneReviews® [Internet], Seattle (WA): University of Washington Feb 23, 2001 [Last update: Sep 2, 2021].
https://www.ncbi.nlm.nih.gov/books/NBK1266/ (accessed 2024-08-26)
6) Yamamoto H, Abe T, Ishiguro S, et al. Clinical Practice Guidelines for Peutz-Jeghers Syndrome in Children and Adults (2020 Edition). Journal of Hereditary Tumors. 2020;20(2):59-78.
7) Gordhandas SB, Kahn R, Sassine D, et al. Gastric-type adenocarcinoma of the cervix in patients with Peutz-Jeghers syndrome:a systematic review of the literature with proposed screening guidelines. Int J Gynecol Cancer. 2022;32(1):79-88. [PMID: 34903560]
8) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1, 2024. (accessed 2024-08-26)

16. Uterine body

Hereditary cancer syndromes with a high lifetime risk of developing endometrial cancer (as well as their causative genes) include Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*), Cowden syndrome/*PTEN* hamartoma tumor syndrome (*PTEN*), Peutz-Jeghers syndrome (*STK11*), polymerase proofreading-associated polyposis (*POLE*, *POLD1*), *MUTYH*-associated polyposis (*MUTYH*), and *NTHL1* tumor syndrome (*NTHL1*).

1. Overview

Endometrial cancer frequently occurs in patients with Lynch syndrome. Since it occurs at a relatively young age, it may be encountered as the first malignant tumor to develop in women with Lynch syndrome. For this reason, endometrial cancer is sometimes referred to as the sentinel cancer of Lynch syndrome. It has been reported that its penetration rate in Lynch syndrome differs depending on the causative gene[1, 2]. The 2024 edition of Clinical Practice Guidelines for Hereditary Colorectal Cancer recommends universal screening for Lynch syndrome using microsatellite instability (MSI) testing or mismatch repair protein immunohistochemistry (MMRIHC) testing for endometrial cancer[3].
Endometrial cancer occurs with a high probability in patients with Cowden syndrome/*PTEN* hamartoma tumor syndrome, patients with Peutz-Jeghers syndrome, and germline pathogenic variant (GPV) carriers of polymerase proofreading-associated polyposis, *MUTYH*-associated polyposis, and *NTHL1* tumor syndrome (*NTHL1*-associated polyposis), in addition to patients with Lynch syndrome.

2. Surveillance

In individuals carrying GPV in genes related to hereditary endometrial cancer, endometrial surveillance is performed with endometrial biopsy[3-9]. Generally, endometrial cytology is not an alternative to endometrial biopsy since it does not have a high accurate diagnosis rate. However, its use is determined at the discretion of the attending physician, as its invasiveness at the time of examination is lower than that of biopsy. The sensitivity and specificity of surveillance with transvaginal ultrasonography have not been demonstrated. In particular, surveillance with transvaginal ultrasonography is not recommended for premenopausal women because the thickness of their endometrium varies greatly depending on the menstrual cycle[10].
The starting age of surveillance differs depending on the causative gene of the hereditary tumor syndrome. Among hereditary tumor syndromes, the earliest starting age of surveillance is recommended for Peutz-Jeghers syndrome, with the recommended starting age of 18–25 years[9-13]. For patients with Lynch syndrome or Cowden syndrome/*PTEN* hamartoma tumor syndrome, surveillance is recommended to be started at the age of 30–35 years[3-9, 14, 15]. There is insufficient evidence for

surveillance for GPV carriers of polymerase proofreading-associated polyposis, *MUTYH*-associated polyposis, and *NTHL1* tumor syndrome (*NTHL1*-associated polyposis). It is important to inform patients that they should undergo testing at a medical institution if they experience irregular genital bleeding or postmenopausal bleeding.

Surveillance testing at intervals of 1–2 years should be considered regardless of the causative gene[3-16].

3. Chemoprevention

Although there have been no large-scale studies on hereditary endometrial cancer, the administration of low-dose oral contraceptive (OC) and low-dose estrogen/progestin (LEP) combination has been reported to reduce the risk of developing endometrial cancer[16].

In patients with Lynch syndrome, it has been reported that the administration of aspirin (600 mg/day) for ≥2 years reduces the occurrence of colorectal cancer, but no significant effect has been observed in patients with Lynch-related cancers, including endometrial cancer. In addition, because aspirin is administered in high doses, there is a risk of gastrointestinal disturbance and bleeding[17]. A study has reported that resistant starch may reduce Lynch-related cancers, but the data must be interpreted with caution due to the large number of subjects who dropped out during the study period[18].

4. Surgical treatment

Regarding risk-reducing surgery, total hysterectomy and bilateral salpingo-oophorectomy are considered for individuals carrying GPV in genes related to hereditary endometrial cancer. The 2024 edition of Clinical Practice Guidelines for Hereditary Colorectal Cancer states that total hysterectomy for women with Lynch syndrome can prevent the development of endometrial cancer, but it has not been shown to reduce the mortality rate. Thus, it requires individualized responses according to family planning such as the desire to have children, comorbidities (systemic diseases, in addition to Lynch syndrome-related tumors such as colorectal cancer), and the type of MMR gene. For patients with Lynch syndrome who require surgery for colorectal cancer, simultaneous implementation of total hysterectomy and bilateral salpingo-oophorectomy should be considered[3, 5, 7-9, 19]. See **Chapter 4** for responses specific to each MMR gene.

If a patient develops endometrial cancer, surgery should be performed in the same manner as that for sporadic endometrial cancer.

5. Drug therapy

In individuals carrying GPV in genes related to hereditary endometrial cancer, drug therapy for endometrial cancer should be administered in the same manner as that for sporadic uterine body cancer. Also, it is known that endometrial cancer in patients with Lynch syndrome exhibits MSI-High, and tumors exhibiting MSI-High are highly sensitive to immune checkpoint inhibitors[20].

■ References

1) Dominguez-Valentin M, Sampson JR, Seppälä TT, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med. 2020;22(1):15-25. [PMID: 31337882]
2) Kempers MJ, Kuiper RP, Ockeloen CW, et al. Risk of colorectal and endometrial cancers in *EPCAM* deletion-positive Lynch syndrome:a cohort study. Lancet Oncol. 2011;12(1):49-55. [PMID: 21145788]
3) Japanese Society for Cancer of the Colon and Rectum (ed.). Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition. Kanehara Publishing Co., Ltd.
4) Weiss JM, Gupta S, Burke CA, et al. NCCN Guidelines® Insights: Genetic/Familial High-Risk Assessment: Colorectal, Version 1. 2021. J Natl Compr Canc Netw. 2021;19(10):1122-32. [PMID: 34666312]
5) Idos G, Valle L. Lynch Syndrome. Adam MP, Feldman J, Mirzaa GM, et al (eds). GeneReviews® [Internet], Seattle (WA): University of Washington Feb 5, 2004 [Last update: Feb 4, 2021]. https://www.ncbi.nlm.nih.gov/books/NBK1211/ (accessed 2024-08-26)
6) Stjepanovic N, Moreira L, Carneiro F, et al. Hereditary gastrointestinal cancers: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30(10):1558-71. [PMID: 31378807]
7) Stoffel EM, Mangu PB, Gruber SB, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines. J Clin Oncol. 2015; 33(2):209-17. [PMID: 25452455]
8) Vangala DB, Cauchin E, Balmaña J, et al. Screening and surveillance in hereditary gastrointestinal cancers:Recommendations from the European Society of Digestive Oncology (ESDO) expert discussion at the 20th European Society for Medical Oncology (ESMO)/World Congress on Gastrointestinal Cancer, Barcelona, June 2018. Eur J Cancer. 2018;104:91-103. [PMID: 30342310]
9) Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223-62; quiz 263. [PMID: 25645574]
10) Dove-Edwin I, Boks D, Goff S, et al. The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary nonpolyposis colorectal carcinoma and familial colorectal carcinoma. Cancer. 2002;94(6):1708-12. [PMID: 11920532]
11) Provenzale D, Gupta S, Ahnen DJ, et al. NCCN Guidelines Insights: Colorectal Cancer Screening, Version 1. 2018. J Natl Compr Canc Netw. 2018;16(8):939-49. [PMID: 30099370]
12) McGarrity TJ, Amos CI, Baker MJ. Peutz-Jeghers Syndrome. Adam MP, Feldman J, Mirzaa GM, et

al (eds). GeneReviews® [Internet], Seattle (WA): University of Washington Feb 23, 2001 [Last update: Sep 2, 2021].
https://www.ncbi.nlm.nih.gov/books/NBK1266/ (accessed 2024-08-26)
13) Yamamoto H, Abe T, Ishiguro S, et al. Clinical Practice Guidelines for Peutz-Jeghers Syndrome in Children and Adults (2020 Edition). Journal of Hereditary Tumors. 2020;20(2):59-78.
14) Yehia L, Eng C. *PTEN* Hamartoma Tumor Syndrome. Adam MP, Feldman J, Mirzaa GM, et al. (eds). GeneReviews® [Internet], Seattle (WA): University of Washington Nov 29, 2001 [Last update: Feb 11, 2021].
https://www.ncbi.nlm.nih.gov/books/NBK1488/ (accessed 2024-08-26)
15) Takayama T, Igarashi M, Ohsumi S, et al. Clinical Practice Guidelines for Cowden Syndrome/*PTEN* Hamartoma Tumor Syndrome in Children and Adults (2020 Edition). Journal of Hereditary Tumors. 2020;20(2):93-114.
16) Gierisch JM, Coeytaux RR, Urrutia RP, et al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers:a systematic review. Cancer Epidemiol Biomarkers Prev. 2013; 22(11):1931-43. [PMID: 24014598]
17) Burn J, Sheth H, Elliott F, et al. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. Lancet. 2020;395(10240):1855-63. [PMID: 32534647]
18) Mathers JC, Elliott F, Macrae F, et al. Cancer Prevention with Resistant Starch in Lynch Syndrome Patients in the CAPP2-Randomized Placebo Controlled Trial: Planned 10-Year Follow-up. Cancer Prev Res (Phila). 2022;15(9):623-34. [PMID: 35878732]
19) Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med. 2006;354(3):261-9. [PMID: 16421367]
20) O'Malley DM, Bariani GM, Cassier PA, et al. Pembrolizumab in Patients With Microsatellite Instability-High Advanced Endometrial Cancer: Results From the KEYNOTE-158 Study. J Clin Oncol. 2022;40(7):752-61. [PMID: 34990208]

17. Ovaries, fallopian tubes, and peritoneum

Hereditary cancer syndromes with a high lifetime risk of developing ovarian cancers, including fallopian tube and peritoneal cancers, (as well as their causative genes) include narrowly defined hereditary breast and ovarian cancer (*BRCA1, BRCA2*), Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*), and individuals who carry a germline pathogenic variant (GPV) in *ATM, BRIP1, PALB2 RAD51C*, or *RAD51D*. MGPT is recommended for all ovarian cancer patients for the purpose of diagnosing hereditary ovarian cancer. Also, genes associated with non-epithelial ovarian tumors have been identified, and there have been reports of an association of Peutz-Jeghers syndrome (*STK11*) with the development of sex cord tumor with annular tubules (SCTAT), as well as an association of *DICER1* syndrome (*DICER1* tumor predisposition) (*DICER1*) with the development of Sertoli-Leydig cell tumor and gynandroblastoma, which are rare sex cord-stromal tumors.

1. Overview

It has been reported that approximately 15% of patients with ovarian, fallopian tube, or peritoneal cancer (hereafter referred to as ovarian cancer) carry GPV in the genes described above[1),2)]. The cumulative risk of ovarian cancer for various cancer susceptibility genes[3)] is as follows: 39–58% for *BRCA1*, 13–29% for *BRCA2*, 10–15% for *RAD51C*, 10–20% for *RAD51D*, 5–15% for *BRIP1*, 2–3% for *ATM*, 3–5% for *PALB2*, 4–20% for *MLH1*, 8–38% for *MSH2*/*EPCAM*, ≤1–13% for *MSH6*, and 1.3–3% for *PMS2* (1–2% in the general population). MGPT is recommended for all ovarian cancer patients for the purpose of diagnosing hereditary ovarian cancer, but of these, *BRCA1* and *BRCA2* (*BRCA1/2*) are the only genes approved by the Pharmaceutical and Medical Device Act in Japan (as of August 2024).

For patients with hereditary ovarian cancer, there is currently no effective method of ovarian surveillance that has been demonstrated to significantly reduce the mortality rate, and risk-reducing salpingo-oophorectomy (RRSO) leads to greater improvement in life prognosis than other methods. Transvaginal ultrasonography or CA125 surveillance is considered if RRSO is not selected or until RRSO is performed.

For the management of hereditary breast and ovarian cancer and Lynch syndrome, please refer to the guidelines released in Japan[4),5)].

2. Methods, starting age, and intervals of surveillance

Ovarian surveillance has not been shown to significantly reduce the mortality rate from ovarian cancer. After clients are made aware that ovarian surveillance is not an alternative to RRSO, transvaginal

ultrasonography and CA125 tumor marker testing can be performed for those who have no intention to undergo RRSO at the time[3-7]. However, since it has been reported that surveillance may increase the rate of early detection as its limited effect, surveillance can be provided if no RRSO is performed at the client's wish[8].

There is no fixed recommended starting age of surveillance. Surveillance should be started at the physician's discretion, taking into consideration the recommended age of RRSO, the age of disease onset in family members, disease risk of each gene, and other factors[3, 7]. Although there is no consensus on the surveillance intervals, it is generally suggested that surveillance be performed every 4 months to 1 year. In addition, if ovarian cancer is suspected during surveillance, contrast-enhanced pelvic MRI should be considered, as it is superior for qualitative diagnosis.

Some patients with *DICER1* syndrome (*DICER1*) develop Sertoli-Leydig cell tumors or gynandroblastoma, and it is recommended that pelvic and abdominal ultrasonography be performed every 6–12 months from the age of 8–10 years until the age of at least 40 years[9, 10].

See **Chapter 4** for gene-specific responses.

3. Chemoprevention

The administration of a combination of low-dose oral contraceptives (OC) and low-dose estrogen/progestin (LEP) generally reduces the risk of ovarian cancer, and multiple reports have agreed that it reduces the risk of ovarian cancer even in individuals carrying GPV in *BRCA1/2*[11]. However, it is not recommended to continue taking OC/LEP beyond the recommended age of RRSO for the purpose of chemoprevention. In addition, there is no consensus on the possibility that long-term administration of OC/LEP increases the risk of developing breast cancer[4].

4. Surgical treatment

RRSO is considered to be the most effective countermeasure for individuals carrying GPV in the causative genes of hereditary ovarian cancer.

According to the 2024 edition of Clinical Practice Guidelines for Hereditary Breast and Ovarian Cancer (HBOC), RRSO should, in principle, be performed under scopic view, and surgical manipulation to prevent intraoperative dissemination should be performed with consideration given to the extent of resection[5]. To make a histopathological diagnosis of RRSO-resected specimens, it is desirable to prepare specimens in accordance with the SEE-FIM protocol[12, 13]. Therefore, RRSO should be performed by a physician specializing in gynecological oncology, in collaboration with a physician specializing in clinical genetics, at a facility where a genetic counseling system and a cooperative system of pathologists are available, and certain facility standards have been established. It is recommended that RRSO be performed for GPV carriers of *BRCA1* at the age of 35–40 years at the completion of childbirth and for GPV carriers of *BRCA2* at the age of 40–45 years if no family members have been diagnosed with ovarian cancer at a young age[3, 7].

For GPV carriers of *RAD51C, RAD51D, BRIP1,* or *PALB2*, European and American guidelines recommend that RRSO be performed at the age of 45–50 years because the risk of developing ovarian cancer increases after the age of 50 years[3, 8].

It has also been stated that GPV carriers of *ATM* should be managed based on family history, as there is insufficient evidence for RRSO[3].

For patients with Lynch syndrome, the 2024 edition of Clinical Practice Guidelines for Hereditary Colorectal Cancer states that risk-reducing surgery for endometrial and ovarian cancers (total hysterectomy and bilateral adnexectomy) is an option to be considered after careful consideration of comorbidities, desire to have children, and other factors. In addition, simultaneous implementation of total hysterectomy and bilateral adnexectomy is considered for patients who require surgery for colorectal cancer[5]. Also, the National Comprehensive Cancer Network (NCCN) guidelines state that total hysterectomy and bilateral salpingectomy should be considered[14]. See **Chapter 4** for gene-specific responses.

In Japan, the FY2020 medical fee revision included partial insurance coverage of RRSO for GPV carriers of *BRCA1/2* among patients with hereditary ovarian cancer, although it was limited to breast cancer-affected individuals (as of August 2024).

5. Drug therapy

Among the repair mechanisms of DNA double-strand breaks, malignant tumors in patients with HBOC exhibit homorogous recombination deficiency (HRD), and thus, cell death can be induced by PARP inhibitors, which disable repair pathways, including single-strand break repair (synthetic lethality). For this reason, the administration of PARP inhibitors can be considered as post-chemotherapy maintenance therapy for initial or recurrent diseases[4, 6]. Additionally, the HRR-related genes *RAD51C, RAD51D, BRIP1, ATM,* and *PALB2* have been shown to be associated with high sensitivity to PARP inhibitors[15].

Platinum preparations commonly used in initial chemotherapy for ovarian cancer inhibit the replication of cancer cells by forming cross-links within DNA strands. Thus, tumors with HRD are thought to be lethal due to a lack of DNA repair, and it has been shown that patients with hereditary ovarian cancer associated with HRD may be highly susceptible[16].

On the other hand, it has been shown that ovarian cancer of individuals carrying GPV in MMR genes is highly sensitive to immune checkpoint inhibitors if the tumor tissue also exhibits MSI-High[17].

■ References

1) Norquist BM, Harrell MI, Brady MF, et al. Inherited Mutations in Women With Ovarian Carcinoma. JAMA Oncol. 2016;2(4):482-90. [PMID: 26720728]
2) Hirasawa A, Imoto I, Naruto T, et al. Prevalence of pathogenic germline variants detected by multigene sequencing in unselected Japanese patients with ovarian cancer. Oncotarget. 2017;8(68):

112258-67. [PMID: 29348823]
3) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment:Breast, Ovarian and Pancreatic. Version 3. 2024. (accessed 2024-08-26)
4) Japan Organization of Hereditary Breast and Ovarian Cancer (ed.). Clinical Practice Guidelines for Hereditary Breast and Ovarian Cancer (HBOC), 2024 Edition. Kanehara Publishing Co., Ltd. 2024.
5) Japanese Society for Cancer of the Colon and Rectum (ed.). Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition. Kanehara Publishing Co., Ltd.
6) Petrucelli N, Daly MB, Pal T. *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer. Adam MP, Feldman J, Mirzaa GM, et al (eds). GeneReviews® [Internet], Seattle (WA): University of Washington Sep 4, 1998 [Last revision: Sep 21, 2023]. https://www.ncbi.nlm.nih.gov/books/NBK1247/ (accessed 2024-08-26)
7) Sessa C, Balmana J, Bober SL, et al. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline. Ann Oncol. 2023;34(1): 33-47. [PMID: 36307055]
8) Rosenthal AN, Fraser LSM, Philpott S, et al. Evidence of Stage Shift in Women Diagnosed With Ovarian Cancer During Phase II of the United Kingdom Familial Ovarian Cancer Screening Study. J Clin Oncol. 2017;35(13):1411-20. [PMID: 28240969]
9) Schultz KAP, Williams GM, Kamihara J, et al. *DICER1* and Associated Conditions: Identification of At-risk Individuals and Recommended Surveillance Strategies. Clin Cancer Res. 2018;24(10):2251-61. [PMID: 29343557]
10) Bakhuizen JJ, Hanson H, van der Tuin K, et al. Surveillance recommendations for *DICER1* pathogenic variant carriers: a report from the SIOPE Host Genome Working Group and CanGene-CanVar Clinical Guideline Working Group. Fam Cancer. 2021;20(4):337-48. [PMID: 34170462]
11) Huber D, Seitz S, Kast K, et al. Use of oral contraceptives in *BRCA* mutation carriers and risk for ovarian and breast cancer: a systematic review. Arch Gynecol Obstet. 2020;301(4):875-84. [PMID: 32140806]
12) Cheng A, Li L, Wu M, et al. Pathological findings following risk-reducing salpingo-oophorectomy in *BRCA* mutation carriers: A systematic review and meta-analysis. Eur J Surg Oncol. 2020;46(1):139-47. [PMID: 31521389]
13) Japan Society of Gynecologic Oncology. Working Group on Cancer Genomic Medicine and Optimization of HBOC Treatment. Views on insurance-covered medical treatment for hereditary breast and ovarian cancer syndrome in obstetrics and gynecology. Revised June 11, 2021. https://jsgo.or.jp/opinion/05.html (reference 2024-08-26)
14) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version

1. 2024. (accessed 2024-08-26)
15) McCabe N, Turner NC, Lord CJ, et al. Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose)polymerase inhibition. Cancer Res. 2006;66(16):8109-15. [PMID: 16912188]
16) Norquist BM, Brady MF, Harrell MI, et al. Mutations in Homologous Recombination Genes and Outcomes in Ovarian Carcinoma Patients in GOG 218: An NRG Oncology/Gynecologic Oncology Group Study. Clin Cancer Res. 2018;24(4):777-83. [PMID: 29191972]
17) Rasmussen M, Lim K, Rambech E, et al. Lynch syndrome-associated epithelial ovarian cancer and its immunological profile. Gynecol Oncol. 2021;162(3):686-93. [PMID: 34275654]

18. Skin

Hereditary cancer syndromes with a high lifetime risk of developing skin tumors (as well as their causative genes) include Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*), Li-Fraumeni syndrome (*TP53*), xeroderma pigmentosum (*XPA, XPB* (*ERCC3*), *XPC, XPD* (*ERCC2*), *XPE* (*DDB2*), *XPF, XPG* (*ERCC5*), *XPV* (*POLH*)), Cowden syndrome/*PTEN* hamartoma tumor syndrome (*PTEN*), familial atypical multiple mole-melanoma syndrome (pancreatic cancer-malignant melanoma syndrome) (*CDKN2A*), basal cell nevus syndrome (*PTCH1, SUFU*), hereditary leiomyomatosis and renal cell cancer syndrome (*FH* tumor predisposition syndrome) (*FH*), and individuals who carry a germline pathogenic variant (GPV) in *CDK4*.

1. Overview

Hereditary skin tumors include malignant melanoma, basal cell carcinoma, squamous cell carcinoma (including actinic keratosis and Bowen's disease as precursor lesions), and sebaceous carcinoma. Commonly occurring carcinomas are characterized by the type of hereditary tumor syndrome, such as basal cell carcinoma in patients with basal cell nevus syndrome, malignant melanoma in patients with familial atypical multiple mole-melanoma syndrome, and malignant melanoma, basal cell carcinoma, and squamous cell carcinoma in patients with xeroderma pigmentosum or Li-Fraumeni syndrome. Non-cancerous benign or hamartoma tumors include keratoacanthoma and sebaceous adenoma in patients with Lynch syndrome, as well as trichilemmoma, acrokeratosis, and papillary lesions of the oral mucosa in patients with Cowden syndrome/*PTEN* hamartoma tumor syndrome.

2. Surveillance methods

In patients with hereditary tumor syndromes, skin surveillance is performed mainly with visual examination. Dermoscopy is useful in diagnosing the benignity or malignancy of suspicious lesions, especially pigmented lesions. If malignancy is suspected by these examinations, a definitive diagnosis is made by biopsy. Surveillance of skin tumors is characterized by an extremely small burden on patients since it can be performed in a short time in an outpatient setting.

3. Starting age of surveillance

Surveillance for xeroderma pigmentosum group A (XPA) should be started from the time of diagnosis in infancy, along with thorough measures against ultraviolet rays, although it depends on the type of hereditary tumor syndrome[1]. Also, it is recommended that surveillance for basal cell nevus syndrome be started at the age of 10 years, as it is often diagnosed in infancy[2]. Few other diseases have a specified starting age of surveillance, but it is recommended that surveillance be started at the age of 18 years for

patients with Li-Fraumeni syndrome and at the age of 10 years for patients with familial atypical multiple mole-melanoma syndrome[3, 4].

4. Surveillance intervals

It is recommended that surveillance be performed every 3–6 months for patients with diseases that frequently develop skin tumors, such as xeroderma pigmentosum and basal cell nevus syndrome[1, 2]. However, for GPV carriers of other hereditary tumor syndromes with a high lifetime risk of developing skin tumors, skin surveillance should generally be performed at intervals of 1 year[3].

5. Surgical treatment

Early-stage skin tumors detected during surveillance can be usually treated by excision under local anesthesia. Also, cryosurgery may be considered as a palliative treatment.

6. Drug therapy

Surgical excision is the first choice of treatment for skin tumors, but topical application of imiquimod has been shown to be effective for actinic keratosis and basal cell carcinoma[5]. Vismodegib, an SMO inhibitor, has been shown to suppress the development of basal cell carcinoma in patients with basal cell nevus syndrome[6]. However, it has not been applied clinically due to its side effects and other issues.

7. Measures against ultraviolet rays

Ultraviolet rays are a representative risk factor for skin cancer, and in Europe and the United States, the general public is educated on appropriate protection measures against ultraviolet rays. Patients with hereditary tumor syndromes need to take measures against ultraviolet rays more thoroughly than others, aside from xeroderma pigmentosum, which also requires thorough measures[3].

■ References

1) Moriwaki S, Kanda F, Hayashi M, et al; Revision Committee for Clinical Practice Guidelines for Xeroderma Pigmentosum. Guidelines of the Japanese Dermatological Association. Clinical Practice Guidelines for Xeroderma Pigmentosum. The Journal of Dermatology. 2015;125(11):2013-22.
2) Fernández LT, Ocampo-Garza SS, Elizondo-Riojas G, et al. Basal cell nevus syndrome:an update on clinical findings. Int J Dermatol. 2022;61(9):1047-55. [PMID: 34494262]
3) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic. Version 3. 2024. (accessed 2024-08-26)
4) UT Southwestern Harold C. Simmons Comprehensive Cancer Center. CDKN2A Mutations: Cancer Risk and Management Recommendations 2020. Last update: Mar, 2020.

https://s3-us-west-2.amazonaws.com/utsw-patientcare-web-production/documents/Familial_Atypical_Mole_Melanoma_CDKN2A.pdf (accessed 2024-08-26)

5) Tran H, Moreno G, Shumack S. Imiquimod as a dermatological therapy. Expert Opin Pharmacother. 2004;5(2):427-38. [PMID: 14996638]

6) Tang JY, Mackay-Wiggan JM, Aszterbaum M, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. N Engl J Med. 2012;366(23):2180-8. [PMID: 22670904].

19. Bone and soft tissue tumors

Hereditary cancer syndromes with a high lifetime risk of developing bone and soft tissue tumors, as well as their causative genes, include Li-Fraumeni syndrome (*TP53*), neurofibromatosis types 1 and 2 (*NF1*, *NF2*), hereditary multiple osteochondromas (*EXT1*, *EXT2*), hereditary retinoblastoma (*RB1*), familial adenomatous polyposis (*APC*), hereditary pheochromocytoma-paraganglioma (PPGL) syndrome (*SDHB*, *SDHC*, *SDHD*), constitutional mismatch repair deficiency (CMMRD) syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*), tuberous sclerosis (*TSC1*, *TSC2*), DICER1 syndrome (*DICER1*), and hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome (*FH*).

1. Overview

Bone and soft tissue tumors are rare cancers with more than 100 subtypes. Many bone and soft tissue tumors that occur as hereditary cancer syndromes are childhood cancers, such as osteosarcoma and embryonal-type rhabdomyosarcoma, and their causative diseases are diverse, including Li-Fraumeni syndrome, neurofibromatosis types 1 and 2, hereditary multiple osteochondromas, hereditary retinoblastoma, familial adenomatous polyposis, hereditary PPGL syndrome, CMMRD syndrome, tuberous sclerosis, *DICER1* syndrome, and HLRCC syndrome. For this reason, it is recommended to perform MGPT to search for the causative gene. Surveillance for bone and soft tissue tumors, if performed, often requires whole-body MRI since they arise from connective tissues in various parts of the body. On the other hand, the incidence rate of bone and soft tissue tumors is often low in patients with various hereditary cancer syndromes, and active surveillance is recommended only when there are findings suggestive of malignancy or when the patient is at an age when tumors commonly develop. In addition, multiple bone and soft tissue tumors occur due to somatic mosaic mutations in some diseases, including neurofibromatosis type 1 (*NF1*), multiple endochondromatosis (*IDH1*, *IDH2*), and McCune-Albright syndrome (*GNAS*), but it should be noted that they are generally not hereditary.

2. Surveillance methods

For patients carrying GPV in the cancer susceptibility genes associated with bone and soft tissue tumors, annual surveillance is generally performed with medical interview and full physical examination, and they undergo additional detailed examinations when findings suggestive of malignancy are obtained[1]. In particular, palpation is crucial in patients with HLRCC syndrome or neurofibromatosis type 1, in whom multiple palpable precursor lesions occur on the body surface, and it is also important to educate patients to seek medical attention promptly when they become aware of the growth of lesions[1, 2].

Because DNA damage repair pathways are impaired in many hereditary tumor syndromes, MRI examination is desirable for imaging without radiation exposure[1], but the appropriate modality should

be selected according to the extent of the search and the location. Trunk MRI is recommended for patients with hereditary PPGL syndrome, in whom gastrointestinal stromal tumors and paragangliomas occur in the trunk[2], and spine MRI is recommended for patients with neurofibromatosis type 2, in whom central nerve lesions commonly occur[3]). However, whole-body MRI covering the limbs is recommended for patients with CMMRD syndrome, Li-Fraumeni syndrome, or neurofibromatosis type 1, in whom bone and soft tissue sarcomas can occur in the trunk or the limbs[1), 4), 5)]. However, it should be noted that whole-body MRI is available only at a limited number of facilities in Japan, can yield false-positive results that lead to overdiagnosis, and requires pediatric patients to be sedated if they cannot remain at rest[1]). Furthermore, gynecological examination and transvaginal ultrasonography are recommended for the early detection of uterine leiomyosarcoma in patients with HLRCC syndrome[5]). Also, abdominal examination, as well as abdominal and pelvic CT or MRI examination, is recommended for patients with familial adenomatous polyposis, since intraperitoneal desmoid tumors are likely to occur within 5 years after abdominal surgery[6]). No appropriate surveillance methods have been proposed for patients with DICER1 syndrome or tuberous sclerosis, in whom bone and soft tissue tumors do not frequently occur.

As mentioned above, bone and soft tissue tumors can occur in various parts of the body, ranging from the skin, muscles, and bone of the limbs to internal organs. Therefore, their surveillance requires collaboration across medical departments.

3. Starting age of surveillance

Surveillance with medical interview and full physical examination should be started when GPV is identified, while invasive testing should be started in consideration of the age when the hereditary tumor syndrome often occurs[1)]. MRI examination is recommended upon identification of GPV, but if the patient is not at high risk of developing cancer, it is acceptable to delay it until the patient is old enough to undergo imaging without sedation[1, 4)]. Patients with neurofibromatosis type 1 require long-term surveillance even in adulthood, and it is recommended to determine the method of surveillance in adulthood after performing whole-body MRI at the age of around 16–20 years[1)].

4. Surveillance intervals

In patients with hereditary tumor syndromes, surveillance for bone and soft tissue tumors is generally performed at intervals of every 2 years, but the surveillance interval should be determined according to the growth rate of tumors that are expected to develop. On the other hand, secondary cancers occur in 21–38% of patients with hereditary retinoblastoma by the age of 50 years[1)], as well as 50% of patients with Li-Fraumeni syndrome, indicating a high risk. Also, the cumulative cancer onset age was reported to be 46 years for men and 31 years for women[4)], showing a lifelong risk of developing secondary cancers. There are no clear criteria for the optimal duration of surveillance, including that for other cancer susceptibility genes.

5. Surgical treatment

In patients with hereditary tumor syndromes, surgical treatment for bone and soft tissue tumors should be administered in the same manner as that for sporadic bone and soft tissue tumors. Multiple cancers are common in patients with Li-Fraumeni syndrome, and there is a risk of developing chemotherapy-associated secondary cancers. Thus, it is desirable to aim for early detection and radical cure with surgical treatment alone[4].

6. Drug therapy

In patients with hereditary tumor syndromes, drug therapy for bone and soft tissue tumors should be administered in the same manner as for sporadic bone and soft tissue tumors. In addition, tumors caused by CMMRD syndrome may exhibit high-frequency microsatellite instability (MSI-High)[1], and the administration of immune checkpoint inhibitors should be considered when indicated. Cancers in patients with CMMRD syndrome are generally resistant to treatment, but the efficacy of alkylating agents and anthracyclines, which are mainly used for bone and soft tissue tumors, is maintained[1].

■ References

1) Ministry of Health, Labour and Welfare Sciences Research Grant, Disease and Disability Control Research Field, Comprehensive Research for the Promotion of Cancer Control, Group for " Research for Implementing Cancer Genome Medical System for Childhood-onset Hereditary Tumors" (Principal Investigator: Tadashi Kumamoto). Clinical Practice Guidance for Childhood-onset Hereditary Tumors. https://mhlw-grants.niph.go.jp/system/files/2019/192021/201908002B_upload/201908002B0008.pdf. (accessed 2024-08-26)

2) Tufton N, Shapiro L, Srirangalingam U, et al. Outcomes of annual surveillance imaging in an adult and paediatric cohort of succinate dehydrogenase B mutation carriers. Clin Endocrinol (Oxf). 2017;86(2):286-96. [PMID: 27678251]

3) GENTURIS ERNorgtrsE. Care pathway-NF2-related schwannomatosis (NF2) version 1.4. accepted Dec 14, 2021. https://www.genturis.eu/l= eng/Assets/20211214_ERN_GENTURIS_Care_Pathway_NF2_v1.4_accepted_disclaimer_new-nomenclature-Version10514.pdf(accessed 2024-08-26)

4) Pediatric Hereditary Tumor Group Guideline Creation Committee. Clinical Practice Guidelines for Li-Fraumeni Syndrome, 2019 Edition. ver. 1.1. 2020.

https://minds.jcqhc.or.jp/common/wp-content/plugins/pdfjs-viewer-shortcode/pdfjs/web/viewer.php?file=https://minds.jcqhc.or.jp/common/summary/pdf/c00607.pdf&dButton=false&pButton=false&oButton=false&sButton=true#zoom=auto&pagemode=none&_wpnonce=3b871a512b (reference 2024-08-26)

5) Patel VM, Handler MZ, Schwartz RA, et al. Hereditary leiomyomatosis and renal cell cancer syndrome: An update and review. J Am Acad Dermatol. 2017;77(1):149-58 [PMID: 8314682]

6) Tomita N, Ishida H, Tanakaya K, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2020 for the Clinical Practice of Hereditary Colorectal Cancer. Int J Clin Oncol. 2021;26(8):1353-419. [PMID: 34185173]

20. Children

For the treatment of hereditary cancer syndromes in pediatric patients, it is practical to use the nine-subgroup classification based on the type of occurring cancer, which was proposed by the Pediatric Cancer Predisposition Working Group of the American Association for Cancer Research. According to the classification, hereditary cancer syndromes and their causative genes are classified as follows: [1] Li-Fraumeni syndrome (*TP53*), [2] neurofibromatosis type 1 (*NF1*), which causes neurofibroma, [3] overgrowth syndromes, including Beckwith-Wiedemann syndrome (11p15.5 imprinting disorder) and WT1-related Wilms tumor (Wilms tumor predisposition) (*WT1*), [4] neuro-oncological syndromes, including hereditary retinoblastoma (*RB1*), [5] gastrointestinal cancer syndromes, including familial adenomatous polyposis (familial polyposis coli) (*APC*), *MUTYH*-associated polyposis (*MUTYH*), juvenile polyposis syndrome (*SMAD4, BMPR1A*), Peutz-Jeghers syndrome (*STK11*), and constitutional mismatch repair deficiency (CMMRD) syndrome (*MLH1, MSH2, MSH6, PMS2*), [6] neuroendocrine syndromes, including multiple endocrine neoplasia type 1 (*MEN1*), multiple endocrine neoplasia type 2 (*RET*), von Hippel–Lindau disease (*VHL*), and hereditary pheochromocytoma and paraganglioma syndrome (*SDHA, SDHAF2, SDHB, SDHC, SDHD, MAX, TMEM127*), [7] leukemia predisposition syndromes, which also include Li-Fraumeni syndrome and CMMRD syndrome, [8] DNA instability syndromes, including telangiectatic cerebellar ataxia (*ATM*), Bloom syndrome (*RECQL3/BLM*), and Nijmegen breakage syndrome (*NBN*), and [9] others, including *DICER1* syndrome (*DICER1* tumor predisposition) (*DICER1*).

For methods, intervals, and starting times of surveillance for each disease, please first refer to the above sections on organ-specific management for adults. If age is not specified in the organ-specific management (i.e., the same testing as that for adults is recommended), it is generally considered that children at the age of ≥8 years are able to undergo MRI without sedation, and in clinical trials, a body weight of 30 kg or an age of 12 years is used as the cutoff point. This suggests that the same organ-specific management as that for adults may be considered for children aged ≥10–12 years. However, children at the age of 10–12 years have large individual differences in mental development. Since continuing surveillance is most important for pediatric patients with hereditary cancer syndromes, it is desirable to have a thorough discussion with the patient and his/her parents or guardians at the time of starting surveillance and to respond to them on a case-by-case basis.

In this section, we discuss the management of pediatric patients, taking into account their differences from adult patients.

1. Overview

GPV in cancer susceptibility genes is detected in approximately 8.5% of pediatric cancer patients who develop cancer before the age of 20 years. Of those patients, however, 4.2% exhibit somatic mosaicism, and only 40% have a family history[1]. Therefore, the possibility of de novo cancer development needs to be considered in pediatric cancer patients.

When planning organ-specific management of hereditary tumor syndromes in children, it is important to note that the type of occurring cancer varies with age, even among those carrying GPV in the same gene. Among patients with DICER1 syndrome, for example, pleuropulmonary blastoma occurs commonly in infants, while multiple thyroid nodules and thyroid carcinomas occur commonly in school-age children, adolescents, and young adults, showing changes in cancer type and organ of occurrence[2]. In patients with Li-Fraumeni syndrome, choroid plexus carcinoma and adrenocortical carcinoma are characteristics of infant patients, while osteosarcoma is more common in adolescence[3]). Furthermore, modifications in developmental processes, including delayed onset of adolescence due to individual cancer treatment, should be taken into consideration, in addition to inherent individual differences in the developmental process of children.

Because testing for pediatric hereditary tumor syndromes needs to be repeatedly performed over a long period of time from childhood, it is desirable to use a testing method that has minimal burden on patients. From the perspective of reducing the burden, the risk of developing secondary cancers and the burden (risk) of general anesthesia (sedation) should be considered when selecting a testing method[4].

Because hereditary cancer syndromes often involve abnormalities in gene function related to DNA damage repair, there is theoretically a concern about increased risk of secondary cancers due to radiation exposure. There has been no clear evidence showing an increase in secondary cancers due to radiation testing in pediatric cancer patients. However, MRI and ultrasonography, which do not involve any radiation exposure, are preferred in children, since an increased risk of brain tumors due to head CT has been previously shown in the general pediatric population[5].

Sedation (anesthesia) is often required for MRI imaging in children under the age of 8 years. The Japan Pediatric Society, the Japanese Society of Pediatric Anesthesiology, and the Japanese Society of Pediatric Radiology have issued joint recommendations on sedation during MRI examination (revised on February 23, 2020)[6]. Using these as references, a management program should be determined for each patient, taking into consideration the risks and benefits. Based on these, this section was written from the perspective of testing method-specific management, rather than organ-specific management, in consideration of the background specific to children. It provides an overview of other tests, including medical examinations, with a focus on MRI and ultrasonography. Also, in children aged ≥8–10 years, it is recommended that tests be performed according to the items of organ-specific management described in this guide, since many tests performed on adults can also be used.

2. Surveillance methods

The surveillance of pediatric hereditary cancer syndromes requires long-term periodic imaging screening from childhood, and radiation exposure should be avoided to the possible extent, due to the issue of radiosensitivity caused by abnormal oncogenes and tumor suppressor genes. Therefore, MRI or ultrasonography is mainly used in imaging screening.

Whole-body MRI is used when the type and location of the occurring cancer cannot be identified, such as in patients with Li-Fraumeni syndrome. The advantages of whole-body MRI are that it does not involve radiation exposure, and that it can image the entire body at once, as it covers a wide imaging area.

Relatively large-scale clinical studies have previously reported that surveillance, including whole-body MRI, was effective in improving overall survival rates among patients with Li-Fraumeni syndrome or CMMRD syndrome[7,8]. In addition, patients with Beckwith-Wiedemann syndrome are known to be at high risk of developing nephroblastoma, hepatoblastoma, and rhabdomyosarcoma in childhood. In particular, patients aged up to 7 years are considered eligible for surveillance for nephroblastoma and hepatoblastoma, and there has been a report on the cost-effectiveness of surveillance for nephroblastoma with abdominal ultrasonography in patients with Beckwith-Wiedemann syndrome[9].

3. Starting age of surveillance

The starting age of surveillance depends on the type of hereditary cancer syndrome. Surveillance should be started based on the starting age for each type and organ of cancer occurrence. If GPV is shared among family members, surveillance should be started before the onset age of the member with the earliest occurrence of the cancer type in the family.

4. Surveillance intervals

Generally, surveillance with whole-body or abdominal MRI is performed at intervals of every 1 to 2 years. For the screening of brain tumors in hereditary retinoblastoma and CMMRD syndrome, head MRI examinations are performed in infants at shorter intervals, approximately every 6 months. Surveillance for pleuropulmonary blastoma in DICER1 syndrome should be performed every 4 to 6 months, as the patients are young children. In children with Li-Fraumeni syndrome under 18 years of age, physical examination, as well as abdominal ultrasonography with consideration for adrenocortical carcinomas, should be performed every 3 to 4 months.

5. Chemoprevention

To date, there has been no practical chemoprevention in pediatric hereditary cancer syndromes. A randomized, controlled trial to examine the cancer prevention effect of metformin in patients with Li-Fraumeni syndrome is scheduled to begin in the United States, the United Kingdom, Canada, and Germany, although it is in the research stage[10].

6. Treatment

There is no specific treatment for pediatric hereditary cancer syndromes, and for some, radiation is known to increase the risk of secondary cancers. In patients with Li-Fraumeni syndrome, there is a concern that radiotherapy increases secondary cancers, and it is desirable to avoid radiotherapy if there are alternative treatment methods that do not compromise treatment outcomes[2]. For example, whole-body irradiation should be avoided during hematopoietic cell transplantation in leukemia patients with Li-Fraumeni syndrome. In addition, the Clinical Practice Guidelines for Breast Cancer state that radiotherapy after breast cancer surgery should be avoided to the possible extent[11]. Also, in the treatment of choroid plexus cancer, surgery or anticancer drug therapy should be selected, if possible, since radiotherapy has been suggested to increase the risk of secondary cancers[12]. If there are no alternative methods, such as postoperative radiotherapy in the treatment of high-risk rhabdomyosarcoma, consideration should be given to reducing the irradiation volume with proton beams and other methods, in order to minimize the risk of secondary cancers[13].

■ References

1) Zhang J, Walsh MF, Wu G, et al. Germline Mutations in Predisposition Genes in Pediatric Cancer. N Engl J Med. 2015;373(24):2336-46. [PMID: 26580448]
2) Nakano Y and Kato M. *Dicer1* syndrome: genetic testing and surveillance. Journal of Hereditary Tumors. 2023;22(3):61-7.
3) Pediatric Hereditary Tumor Group Guideline Creation Committee. Clinical Practice Guidelines for Li-Fraumeni Syndrome, 2019 Edition. ver. 1.1. 2020. https://minds.jcqhc.or.jp/common/wp-content/plugins/pdfjs-viewer-shortcode/pdfjs/web/viewer.php?file=https://minds.jcqhc.or.jp/common/summary/pdf/c00607.pdf&dButton=false& pButton=false& oButton= false& sButton= true#zoom= auto& pagemode=none&_ wpnonce=3b871a512b (reference 2024-08-26)
4) Hattori H. Hereditary tumors and surveillance. J Jpn Pediatr Soc. 2023;127(4):557-66. 5) Hauptmann M, Byrnes G, Cardis E, et al. Brain cancer after radiation exposure from CT examinations of children and young adults: results from the EPI-CT cohort study. Lancet Oncol. 2023;24(1):45-53. [PMID: 36493793]
5) Hauptmann M, Byrnes G, Cardis E, et al. Brain cancer after radiation exposure from CT examinations of children and young adults：results from the EPI-CT cohort study. Lancet Oncol. 2023；24（1）：45-53.［PMID：36493793］
6) Japan Pediatric Society, Japanese Society of Pediatric Anesthesiology, and Japanese Society of Pediatric Radiology. Joint recommendations on sedation during MRI examinations. J Jpn Pediatr Soc. 2020;124(4):771-805.

7) Villani A, Shore A, Wasserman JD, et al. Biochemical and imaging surveillance in germline *TP53* mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. Lancet Oncol. 2016;17(9):1295-305. [PMID: 27501770]
8) Durno C, Ercan AB, Bianchi V, et al. Survival Benefit for Individuals With Constitutional Mismatch Repair Deficiency Undergoing Surveillance. J Clin Oncol. 2021;39(25):2779-90. [PMID: 33945292]
9) Mussa A, Duffy KA, Carli D, et al. The effectiveness of Wilms tumor screening in Beckwith-Wiedemann spectrum. J Cancer Res Clin Oncol. 2019;145(12):3115-23. [PMID: 31583434]
10) Dixon-Zegeye M, Shaw R, Collins L, et al. Cancer Precision-Prevention trial of Metformin in adults with Li Fraumeni syndrome (MILI) undergoing yearly MRI surveillance: a randomised controlled trial protocol. Trials. 2024;25(1):103. [PMID: 38308321]
11) Japanese Breast Cancer Society Clinical Practice Guidelines Committee. Review 2: Cases for which radiotherapy is not recommended after breast surgery. Clinical Practice Guidelines for Breast Cancer, 2022 Edition, Treatment Edition. Japanese Breast Cancer Society, 2022. https://jbcs.xsrv.jp/guideline/2022/h_index/s2/ (reference 2024-08-26)
12) Bahar M, Kordes U, Tekautz T, et al. Radiation therapy for choroid plexus carcinoma patients with Li-Fraumeni syndrome: advantageous or detrimental? Anticancer Res. 2015;35(5): 3013-7. [PMID: 25964589]
13) Thariat J, Chevalier F, Orbach D, et al. Avoidance or adaptation of radiotherapy in patients with cancer with Li-Fraumeni and heritable TP53-related cancer syndromes. Lancet Oncol. 2021;22(12):e562-74. [PMID: 34856153]

CHAPTER 4. Causative genes of hereditary tumor syndromes and their management

Overview of Chapter 4

Chapter 4 is intended to present, in a one-page fact sheet format for each gene, medical management information on preventive interventions. These are provided to individuals in whom GPVs have been detected in cancer susceptibility genes, which are responsible for specific genetic tumor syndromes, and are necessary for the clinical implementation of MGPT.

1. Target genes

In this chapter, we selected 56 genes associated with hereditary tumor syndromes, based on their coverage and publication status in domestic and international practice guidelines. We will continue to review these genes on an ongoing basis, adding or removing information as new evidence emerges regarding cancer risk, the clinical utility of surveillance, the usefulness of prophylactic or risk-reducing surgeries, and other relevant factors.

1. 56 genes covered in this chapter (in alphabetical order)

APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, DICER1, EPCAM, FLCN, FH, GALNT12, GREM1, HOXB13, MAX, MEN1, MET, MLH1, MSH2, MSH3, MSH6, MUTYH, NF1, NF2, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, RB1, RET, RNF43, RPS20, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, STK11, TMEM127, TP53, TSC1, TSC2, VHL, WT1

2. Description

1. Gene name

In principle, we listed the gene names (symbols) used by the National Center for Biotechnology Information (NCBI).

2. Disease name

The following points should be noted regarding the names of hereditary tumor syndromes used in this chapter:

・In principle, we listed the names of the phenotypes that are associated with the cancer onset risk posed by the presence of GPV (OMIM numbers), as used in OMIM (https://www.omim.org/).

・As the phenotype for *ATM*, for example, we listed “Breast cancer, susceptibility to (114480),” which indicates a dominant inheritance pattern of cancer development, rather than “Ataxia-telangiectasia (208900),” which indicates a recessive inheritance pattern. If available, we also listed Japanese disease names found in the Japanese version of GeneReviews (GRJ: http://grj.umin.jp).

・The disease names listed in accordance with the above principles may differ from the names used commonly in Japan today or the names that have been used globally in recent years.

3. Inheritance pattern

We listed the inheritance patterns that correspond to the phenotypes associated with the risk of cancer onset.

4. GPV frequency (frequency of carriers of germline pathological variants)

GPV frequency indicates the prevalence of GPV carriers in a population cohort, without considering the presence or absence of cancer. For this reason, we, in principle, adopted only data generated from studies with generalizable sample sizes, for example, 10,000 or more healthy individuals, giving priority to data from Japanese cohorts when available. If data from Japanese cohorts were not available, we used data from overseas studies, and in such cases, information on the cohort population, for example, the United Kingdom or other countries, was provided.

5. Risk of cancer onset (penetration rate)

In principle, we focused on malignant solid tumors and adopted only those for which the absolute risk (%) had been reported as onset frequency. Data based solely on odds ratios or stratified only by gender were not adopted. We included only studies with a generalizable number of GPV cases, for example, 100 or more, and listed the evaluation periods of onset frequency, for example, under 70 years of age, when available. Studies with small case numbers, such as case reports, were included in the *Supplementary Information* section. Information that could not be verified in the original paper was not adopted, even if described in the guidelines. Additionally, the risk of developing benign tumors was listed where relevant.

6. Domestic clinical practice guidelines

We listed the names of guidelines and publishing societies, as well as years of publication.

7. Clinical management recommended by domestic clinical practice guidelines

In principle, we listed recommended methods of clinical management and noted any clinical management other than recommended methods, such as methods that should be considered conditionally.

8. Clinical management recommended by international clinical practice guidelines

When overseas guidelines are available, the clinical management methods described in them are listed. If domestic guidelines also exist, only methods not included in the domestic guidelines are additionally described, along with any items considered necessary to note. In cases where the content of domestic and international guidelines is the same, a statement is provided to indicate that no additional items are recommended.

1 *APC*

2

Disease	FAMILIAL ADENOMATOUS POLYPOSIS 1; FAP1 (OMIM 175100) (GRJ *APC*-related polyposis)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	3/37,592 persons[1], 1/23,705 persons[2]
Risk of cancer onset (penetration rate)	Colorectal cancer: 100% (approximately 50% in patients in mid-40s and nearly 100% in patients aged ≥60 years)[3], duodenal carcinoma: approximately 7.7%[4] and <1–10%[5, 6], gastric cancer: 0.6–7%[5, 7, 8], desmoid tumor: 10–15%[9] and 12.8–23.8%[10-15], thyroid cancer: 1.3–11.4% (mostly women)[16-20], adrenocortical tumor: 7.4–16%[21-23], brain tumor (medulloblastoma is most common): 1%[24, 25], hepatoblastoma: 0.4–2.5%[26-30]
Domestic clinical practice guidelines	Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition. Japanese Society for Cancer of the Colon and Rectum (ed.)[31]
Clinical management recommended by domestic clinical practice guidelines	**Colorectal adenoma/carcinoma**: For patients with classic FAP[*1], colonoscopy is performed every 1–2 years after around 10 years of age. For patients with attenuated FAP (AFAP)[*2], colonoscopy is performed every 2–3 years, beginning in late adolescence (around 18–20 years of age). As definitive treatment, prophylactic colorectal resection should be performed before the onset of colorectal cancer. **Residual rectal adenoma**: Colonoscopy and resection or cauterization of adenoma are performed annually after total colon resection and ileal pouch anal (tube) anastomosis, or every 6 months after total colectomy and ileorectal anastomosis (depending on age and adenoma density). **Duodenal adenoma/carcinoma** (including those in the papillary region): Upper gastrointestinal endoscopy is performed either at the time of colorectal resection or at 20–25 years of age, whichever occurs first. Subsequently, it should be repeated at regular intervals, with the frequency determined by the severity of the adenoma. **Gastric adenoma/carcinoma**: Upper gastrointestinal endoscopy is performed annually (or concurrently with duodenal examination). **Thyroid cancer**: For female patients, baseline ultrasonography is started in the late teen years (at intervals of 2–5 years if findings are normal), and the interval is shortened if the patient has a family history of thyroid cancer. **Intra-abdominal desmoid tumor**: Abdominal palpation is performed annually. After colorectal resection, CT/MRI of the abdomen/pelvis is performed every 3 years, especially if the patient has a family history of desmoid tumor. **Jejunal and ileal adenoma/carcinoma**: Observation is made promptly during the imaging test of desmoid tumor (CT/MRI).

Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] **Intra-abdominal desmoid tumor**: Abdominal imaging is performed immediately if the patient exhibits abdominal symptoms. For patients with symptomatic desmoid, abdominal CT/MRI (with and without contrast) is performed, although it does not need to be performed every year (to be considered). **Gastric/duodenal carcinoma**: Surveillance should begin at an earlier age in patients with a family history of duodenal adenoma or carcinoma. The surveillance interval is determined by the Spigelman score for duodenal polyps, and by polyp size and histological type for gastric polyps. Referral to a specialized medical institution or consideration of surgical resection is also recommended. **Brain tumor**: Neurological symptoms, if any, should be promptly reported to the primary care physician. **Jejunal and ileal adenoma/carcinoma**: Small-bowel capsule/endoscopy is considered if the patient has progressive duodenal polyposis. **Hepatoblastoma**: Hepatic palpation, abdominal ultrasonography, and AFP measurements are performed every 3–6 months until 5 years of age (to be considered).
Supplementary information	Based on the disease frequency, the incidence of familial adenomatous polyposis at birth was estimated to be 1/17,400 persons[33]. A GPV in the promoter 1B region of the APC gene causes gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), an autosomal dominant syndrome characterized by gastric cancer arising in the background of fundic gland polyposis. Polyposis of the duodenum or large intestine does not occur. Although prophylactic gastrectomy has been reported overseas, the evidence is limited to family-level case reports[34].

＊1. Classic (typical) FAP: Based on the number of colorectal adenomas, classic FAP is classified into dense type with >1,000 (or 2,000) adenomas and non-dense type with 100–1,000 (or 2,000) adenomas.

＊2. Attenuated FAP (AFAP): Patients with AFAP have approximately 10 to <100 adenomas. It is also referred to as mild FAP, dilute FAP, or sporadic FAP, and there is no set term for the condition.

ATM

Disease	BREAST CANCER {Breast cancer, susceptibility to} (OMIM 114480)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.3–0.41%[1, 35], 0.3% (overseas)[36]
Risk of cancer onset (penetration	Breast cancer: 17–30%[36, 37] (see 'Supplementary information 1'), pancreatic cancer: unknown (see 'Supplementary information 2')

rate)	
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3. 2024-February 12, 2024[38] **Breast cancer**: Mammography is performed annually starting at 40 years of age, and breast MRI with and without contrast is performed annually starting at 30–35 years of age (to be considered). **Pancreatic cancer**: For GPV carriers who have at least one first- or second-degree relative with a family history of pancreatic cancer, surveillance (contrast-enhanced MRI/MRCP and/or EUS) is performed annually starting at 50 years of age (or 10 years earlier than the onset age of the affected family member with the earliest onset). **Prostate cancer**: Surveillance is started at 40 years of age (to be considered).
Supplementary information	1. Among individuals with c.7271T>G, the risk of developing breast cancer by 70 years of age was reported to be 52%[39]. 2. The risk of developing pancreatic cancer was estimated to be 9.5% (up to 80 years of age)[40]. 3. Other cancer types whose penetration rate is unknown, although their correlation with onset risk has been pointed out: ovarian cancer and prostate cancer 4. There is insufficient evidence on RRM for breast cancer, and patients are managed based on family history. 5. There is insufficient evidence on RRSO for ovarian cancer, and patients are managed based on family history.

1

AXIN2

Disease	OLIGODONTIA-COLORECTAL CANCER SYNDROME; ODCRCS (OMIM 608615)
Inheritance pattern	Autosomal dominant inheritance[41]
GPV frequency	Unknown (see 'Supplementary information')
Risk of cancer onset (penetration rate)	Unknown (see 'Supplementary information')
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] **Colorectal cancer**: Starting at 25–30 years of age, colonoscopy is performed every 2–3 years for patients without polyps and every 1–2 years for patients with polyps. Surgery is considered if polyps become unmanageable by colonoscopy.
Supplementary information	A study in which genetic testing was performed on 3,009 patients with solid tumors, one (0.03%) patient was carrying GPV in *AXIN2*[42]. However, the frequency of GPV carriers in the general population is unknown. The NCCN guidelines state that the risk of developing colorectal cancer among

	AXIN2 GPV carriers is unknown ('insufficient data to define')[32].

1

BAP1

Disease	TUMOR PREDISPOSITION SYNDROME 1; TPDS1 (OMIM 614327) (GRJ *BAP1* tumor predisposition syndrome)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	1/26,837 persons[43]
Risk of cancer onset (penetration rate)	*BAP1*-inactivated melanocytic tumor: 9.0%[44], uveal malignant melanoma: 33.1–28.0%[44-46], malignant mesothelioma: 22.6–22.0%[44-46], cutaneous malignant melanoma: 28.7–13.0%[44-46], renal cell carcinoma: 10.3–5.7%[44-46], basal cell carcinoma: 6.5%[44]
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Kidney Cancer. Version 3. 2024-Mar 11, 2024[47] **Renal cell carcinoma**: MRI with and without contrast (preferreed) or CT is performed every 2 years starting at 30 years of age.
Supplementary information	Rai et al.[46] recommended the following: **Uveal malignant melanoma**: Mydriatic and fundus examinations are performed annually starting at 11 years of age. **Cutaneous malignant melanoma**: Total-body skin examination is performed by a

	dermatologist annually starting at 20 years of age. Star et al.[48] recommended the following: **Uveal malignant melanoma**: Medical examination is performed by a specialist physician annually starting at 16 years of age. **Malignant mesothelioma**: Abdominal and chest examinations are performed annually starting at 30 years of age. **Cutaneous malignant melanoma**: Total-body skin examination is performed by a dermatologist every 6 months starting at 18 years of age.

1

BARD1

Disease	BREAST CANCER {Breast cancer, susceptibility to} (OMIM 114480)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.05%[1], 0.11% (overseas)[49]
Risk of cancer onset (penetration rate)	Unknown (see 'Supplementary information')
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3. 2024-February 12, 2024[38] **Breast cancer**: Mammography is performed annually starting at 40 years of age, and breast MRI with and without contrast is performed annually starting at 40 years of age (to be considered). ※The starting age of MRI is determined based on risk factors (family history, age, and breast density) and other information.
Supplementary information	Although an association with ovarian cancer has been reported, there is insufficient evidence on the onset risk.

	For the *ATM, BARD1, CHEK2, RAD51C,* and *RAD51D* genes combined, the penetration rate (absolute risk) of breast cancer up to 80 years of age was estimated to be 17–30%, indicating a moderate risk[36].

1

BLM

Disease	Not applicable
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	Unknown
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] There is insufficient evidence on the surveillance for colorectal cancer in *BLM* heterozygous patients, and they should be managed based on family history.
Supplementary information	Cancer types whose penetration rate is unknown, although their correlation with the onset risk in the heterozygous state has been pointed out: colorectal cancer

1

BMPR1A

Disease	JUVENILE POLYPOSIS SYNDROME; JPS (OMIM 174900) (GRJ juvenile polyposis syndrome)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	The overall risk of cancer onset in patients with juvenile polyposis syndrome (JPS) is 86.2% (gastric cancer: 73.0%, colorectal cancer: 51.1%, small intestinal cancer: rare, pancreatic cancer: rare)[50].
Domestic clinical practice guidelines	Clinical Practice Guidelines for Juvenile Polyposis Syndrome in Children and Adults (2020 Edition)[51]
Clinical management recommended by domestic clinical practice guidelines	**Gastrointestinal (malignant) tumor**: For suspected cases, upper gastrointestinal endoscopy and colonoscopy are performed 12–15 years of age. Responses taken after definitive diagnosis vary depending on the number of polyps and the phenotype, such as gastric- and colorectal-localized types, and upper gastrointestinal endoscopy and colonoscopy are performed every 1–3 years. Surveillance is started early if the patient exhibits symptoms caused by polyps. If small-intestinal bleeding or protein-losing gastroenteropathy is suspected, balloon small-intestinal endoscopy, capsule endoscopy, or CT enterography is performed. Polyps with a size of ≥5 mm are treated with endoscopic resection, and partial resection of the intestinal tract is considered for patients with multiple polyps that cannot be managed with endoscopic therapy.
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes (2015)[52] There are no additional recommended items.

Supplementary information	In a meta-analysis of JPS patients, only one of 203 *BMPR1A* GPV carriers was found to have gastric cancer[53]. *BMPR1A* GPV carriers have a lower risk of developing gastric cancer than *SMAD4* GPV carriers[54]. Some patients with partial deletions of 10q22-23 involving *PTEN* or *BMPR1A* have clinical features of both Cowden syndrome/*PTEN* hamartoma tumor syndrome and JPS and present with a clinical picture of severe early-onset polyposis syndrome[55]. Reference #50 is a domestic case report review of JPS.

1

BRCA1

Disease	BREAST-OVARIAN CANCER, FAMILIAL, SUSCEPTIBILITY TO, 1; BROVCA1 (OMIM 604370) (GRJ *BRCA1*- and *BRCA2*-related hereditary breast and ovarian cancer)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.07%[1], 0.11–0.12% (overseas)[36, 49]
Risk of cancer onset (penetration rate)	Breast cancer: >60%[37, 56-60], ovarian cancer: 39–58%[61], pancreatic cancer: ≤5%[62], prostate cancer: 7–26%[63]
Domestic clinical practice guidelines	Clinical Practice Guidelines for Hereditary Breast and Ovarian Cancer (HBOC), 2024 Edition. Japan Organization of Hereditary Breast and Ovarian Cancer[64]
Clinical management recommended by domestic clinical practice guidelines	**Breast cancer**: [Cancer-affected individuals] No recommended age has been specified for contralateral risk-reducing mastectomy (CRRM). No starting age has been specified for surveillance with contrast-enhanced breast MRI. [Cancer-free individuals] No recommended age has been specified for bilateral risk-reducing mastectomy (BRRM). It is assumed that surveillance with contrast-enhanced breast MRI is performed annually, with no starting age specified. **Ovarian cancer**: No recommended age has been specified for risk-reducing salpingo-oophorectomy (RRSO). No starting age has been specified for the administration of a low-dose oral contraceptive (OC) or a low-dose estrogen/progestin combination (conditionally recommended). **Pancreatic cancer**: Surveillance with MRI/MRCP or ultrasound endoscopy is performed. (It is considered even for patients aged <50 years, depending on the risk, at intervals of 6–12 months.) **Prostate cancer**: Surveillance with PSA is started at 40 years of age, with no implementation frequency specified.
Clinical management recommended by international clinical practice guidelines Only items	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3. 2024-February 12, 2024[38] **Breast cancer**: Breast awareness starts at 18 years of age. Breast examination is performed every 6–12 months starting at 25 years of age. Breast MRI with and without contrast is performed annually between the ages of 25 and 29 years. Mammography and breast MRI with and without contrast are performed annually between the ages of 30 and 75 years. For individuals aged ≥75 years, surveillance is performed on a case-by-case basis. Consultation for RRM is provided (no starting

not described in domestic practice guidelines are listed.	age or implementation frequency has been specified). For male patients, self-examination training and education are started at 35 years of age, and breast examination is performed annually starting at 35 years of age. **Ovarian cancer**: RRSO is performed 35–40 years of age. Estrogen/progestin combination (e.g., oral contraceptive) is orally administered for ovulation suppression (to be considered). **Pancreatic cancer**: For GPV carriers who have at least one first- or second-degree relative with a family history of pancreatic cancer, surveillance (contrast-enhanced MRI/MRCP and/or EUS) is performed annually starting at 50 years of age (or 10 years earlier than the onset age of the affected family member with the earliest onset) (to be considered). **Prostate cancer**: Surveillance (with PSA and rectal examinations) is performed annually starting at 40 years of age (to be considered).
Supplementary information	In men, the risk of developing breast cancer by 70 years of age was reported to be 0.2–1.2% (overseas)[62, 65].

1

BRCA2

Disease	BREAST-OVARIAN CANCER, FAMILIAL, SUSCEPTIBILITY TO, 2; BROVCA2 (OMIM 612555) (GRJ *BRCA1*- and *BRCA2*-related hereditary breast and ovarian cancer)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.21%[1], 0.14–0.27% (overseas)[36, 49]
Risk of cancer onset (penetration rate)	Breast cancer: >60%[37, 56-60], ovarian cancer: 13–29%[61], pancreatic cancer: 5–10%[62], prostate cancer: 19–61%[63, 66]
Domestic clinical practice guidelines	Clinical Practice Guidelines for Hereditary Breast and Ovarian Cancer (HBOC), 2024 Edition. Japan Organization of Hereditary Breast and Ovarian Cancer[64]
Clinical management recommended by domestic clinical practice guidelines	**Breast cancer**: [Cancer-affected individuals] No recommended age has been specified for contralateral risk-reducing mastectomy (CRRM). No starting age has been specified for surveillance with contrast-enhanced breast MRI. [Cancer-free individuals] No recommended age has been specified for bilateral risk-reducing mastectomy (BRRM). It is assumed that surveillance with contrast-enhanced breast MRI is performed annually, with no starting age specified. **Ovarian cancer**: No recommended age has been specified for risk-reducing salpingo-oophorectomy (RRSO). No starting age has been specified for the administration of a low-dose oral contraceptive (OC) or a low-dose estrogen/progestin combination (conditionally recommended). **Pancreatic cancer**: Surveillance with MRI/MRCP or ultrasound endoscopy is performed. (It is considered even for patients aged <50 years, depending on the risk, at intervals of 6–12 months.) **Prostate cancer**: Surveillance with PSA is started at 40 years of age, with no implementation frequency specified.
Clinical management recommended by international clinical practice guidelines	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3. 2024-February 12, 2024[38] **Breast cancer**: Breast awareness starts at 18 years of age. Breast examination is performed every 6–12 months starting at 25 years of age. Breast MRI with and without contrast is performed annually between the ages of 25 and 29 years. Mammography and breast MRI with and without contrast are performed annually between the ages of 30 and 75 years. For individuals aged ≥75 years, surveillance is performed on a case-by-case basis. Consultation for RRM is provided (no starting age or implementation frequency has been specified).

Only items not described in domestic practice guidelines are listed.	For male patients, self-examination training and education are started at 35 years of age, and breast examination is performed annually starting at 35 years of age. Mammography is performed annually starting at 50 years of age (or 10 years earlier than the onset age of the affected family member with the earliest onset) (to be considered). **Ovarian cancer**: RRSO is performed by the age of 40–45 years. Estrogen/progestin combination (e.g., oral contraceptive) is orally administered for ovulation suppression (to be considered). **Pancreatic cancer**: For GPV carriers who have at least one first- or second-degree relative with a family history of pancreatic cancer, surveillance (contrast-enhanced MRI/MRCP and/or EUS) is performed annually starting at 50 years of age (or 10 years earlier than the onset age of the affected family member with the earliest onset). **Prostate cancer**: Surveillance (with PSA and rectal examinations) is performed annually starting at 40 years of age.
Supplementary information	In men, the risk of developing breast cancer by 70 years of age was reported to be 1.8–7.1% (overseas)[62, 65, 67].

1

BRIP1

Disease	BREAST CANCER {Breast cancer, early-onset, susceptibility to} (OMIM 114480)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.13%[1], 0.15% (overseas)[36]
Risk of cancer onset (penetration rate)	Breast cancer: no sufficient data available, ovarian cancer: 5–15%[68, 69]
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3. 2024-February 12, 2024[38] **Breast cancer**: No sufficient data is available. **Ovarian cancer**: Risk-reducing salpingo-oophorectomy is started at 45–50 years of age (recommended).
Supplementary information	—

CDH1

Disease	DIFFUSE GASTRIC AND LOBULAR BREAST CANCER SYNDROME; DGLBC (OMIM 137215) (GRJ hereditary diffuse gastric cancer)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.01%[1)]
Risk of cancer onset (penetration rate)	Unknown (see 'Supplementary information')
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	1. NCCN Guidelines® Gastric Cancer. version 1. 2024-March 7, 2024[70)] 2. NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3. 2024-February 12, 2024[38)] 3. NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32)] **Gastric cancer**: Prophylactic total gastrectomy is performed by the age of 18–40 years. Baseline endoscopy is required before prophylactic total gastrectomy. Proximal and distal instant frozen histological diagnosis should be performed. If prophylactic total gastrectomy is not considered, upper gastrointestinal endoscopy and random biopsy are performed every 6–12 months. If the patient has a family history of gastric cancer with onset at <25 years of age, prophylactic gastrectomy is performed, even for patients aged <18 years. Patients are presented with the options of total gastrectomy or endoscopic surveillance, and their decision-making is supported by medical professionals, including multidisciplinary experts, taking into consideration the benefits/disadvantages, preferences of the patient, and other factors. **Breast cancer**: Mammography is performed annually starting at 30 years of age. Breast MRI with and without contrast is performed annually starting at 30 years of

	age (to be considered). 4. Blair VR, McLeod M, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical practice guidelines. Lancet Oncol. 2020; 21: e386-e397.[71] **Gastric cancer**: For patients with a family history of HDGC, prophylactic total gastrectomy is performed at 20–30 years of age. If no prophylactic total gastrectomy is performed, upper gastrointestinal endoscopy is performed annually. Eradication of *H. pylori* infection is performed, if present. **Breast cancer**: Contrast-enhanced breast MRI is performed annually starting at 30 years of age. Mammography is performed for patients aged ≥40 years. Bilateral risk-reducing mastectomy is performed for patients aged 30–59 years (to be considered). If a patient carries VUS in *CDH1* or has been clinically diagnosed with HDGC-like syndrome, upper gastrointestinal endoscopy is performed at least every 2 years for the patient and his/her first-degree relatives (to be considered).
Supplementary information	The risk of cancer onset in *CDH1* GPV carriers has been estimated as follows: gastric cancer: 42–67% (men) and 33–83% (women)[72, 73], breast cancer: 39–55% (women)[72, 73]. Responses with prophylactic total gastrectomy vary depending on the guidelines.

1

CDK4

Disease	MELANOMA, CUTANEOUS MALIGNANT, SUSCEPTIBILITY TO, 3; CMM3 (OMIM 609048)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	<0.01%[1)]
Risk of cancer onset (penetration rate)	Malignant melanoma: 74%[74, 75)]
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	None
Supplementary information	GPV has been reported only at codon R24 (R24C, R24H, and R24L), which is located in the binding domain for the CDKN2A protein[74, 75)]. It has been estimated that germline variants in *CDK4* are detected in approximately 5% of familial melanoma patients[76, 77)].

	There have been reports on fewer than 20 families[74, 75, 78]. There have been reports of the occurrence of pancreatic cancer, breast cancer, lung cancer, colorectal cancer, lymphoma, cervical cancer, gastric cancer, and other cancer types[75, 78].

1

CDKN2A

Disease	MELANOMA-PANCREATIC CANCER SYNDROME (OMIM 606719)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.01%[1)]
Risk of cancer onset (penetration rate)	Malignant melanoma: 28% (≤70 years of age)[79)] and 68.3% (≤80 years of age)[80)], pancreatic cancer: 17–20.7%[81, 82)]
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines® Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3. 2024-February 12, 2024[38)] **Pancreatic cancer**: For GPV carriers who have at least one first- or second-degree relative with a family history of pancreatic cancer, surveillance (contrast-enhanced MRI/MRCP and/or EUS) is performed annually starting at 40 years of age (or 10 years earlier than the onset age of the affected family member with the earliest onset) (to be considered). If the patient carries GPV for isoforms of definite biologic significance, total-body examination (photography and dermoscopy) is performed by a dermatologist every 2 years.
Supplementary information	It has been estimated that GPV in *CDKN2A* is detected in 20–40% of patients with familial melanomas[77)], as well as in 1.5–6% of all melanoma patients, since 7–15% of malignant melanoma cases are familial. It is detected in 0.3% of pancreatic cancer patients[83)]. Also, its detection has been reported in patients with sarcoma, breast cancer, lung cancer, squamous cell

	carcinoma of the head and neck, and nervous system tumors (including astrocytoma)[74, 84]. Of the $p14^{ARF}$ and $p16^{INK4A}$-encoding exons 1 of *CDKN2A*, the deletion of 1β encoding the latter or the entire *CDKN2A* was reported to be associated with the development of nervous system tumors (including astrocytoma)[74, 84].

CHEK2

Disease	TUMOR PREDISPOSITION SYNDROME 4; TPDS4 (OMIM 609265)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.09–0.12%[1, 85, 86], 0.42% (overseas)[49]
Risk of cancer onset (penetration rate)	Breast cancer: 20–44%[49, 87-90], colorectal cancer: 6.0–7.2% (up to 80 years of age)[91]
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	1. NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3. 2024-February 12, 2024[38] 2. NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] 3. NCCN Guidelines®, Prostate Cancer Early Detection. Version 2. 2024-Mar 6, 2024[92] **Breast cancer**: Mammography is performed annually starting at 40 years of age. Breast MRI with and without contrast is performed annually starting at 30–35 years of age (to be considered). **Prostate cancer**: PSA is measured annually starting at 40 years of age (to be considered).
Supplementary information	It has been reported that the onset risk varies depending on the position of the variant. Most studies have focused on c.1100delC (p.T367fs) and c.470T>C (p.I157T), which have a moderate and low risk of breast cancer, respectively. Medical management policies should be selected based on the risk of related cancers in each variant[91, 93].

1

DICER1

Disease	GOITER, MULTINODULAR 1, WITH OR WITHOUT SERTOLI-LEYDIG CELL TUMORS; MNG (OMIM 138800) and/or PLEUROPULMONARY BLASTOMA; PPB (OMIM 601200) (GRJ *DICER1* tumor predisposition)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	1/3,700–10,600 persons (overseas)[94, 95]
Risk of cancer onset (penetration rate)	Pleuropulmonary blastoma (PPB): 15–28%[96], ovarian cord-stromal tumor: <10%[97], thyroid cancer: 2–4%[96, 98], cystic nephroma: 6–10%[96], ciliary medulloblastoma: <3%[99]
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	1. DICER1 and Associated Conditions: Identification of At-risk Individuals and Recommended Surveillance Strategies (2018)[100] 2. Surveillance recommendations for DICER1 pathogenic variant carriers: a report from the SIOPE Host Genome Working Group and CanGene-CanVar Clinical Guideline Working Group (2021)[101] While promoting the patient's and family's understanding of *DICER1*-related symptoms, examinations, and medical interviews for *DICER1*-related tumors are performed at least annually starting until 20 years of age[100, 101]. **Chest**: Chest X-ray is performed every 4–6 months between the ages of 0 and 6–8 years[100, 101], and fetal ultrasonography is performed in the third trimester of pregnancy[101]. **Thyroid:** Thyroid ultrasonography is performed every 3 years (or according to symptoms and findings) between the ages of 8 and 40 years (or with no upper age limit)[100, 101]. Thyroid function is evaluated at the time of pregnancy[101]. **Kidneys**: Abdominal ultrasonography is performed every 6 months between the ages

	of 0 and 6–8 years and annually between the ages of 9 and 12 years[100]. If the diagnosis is made after the age of 6 years, ultrasonography is performed once (to be considered)[101]. **Female reproductive organs**: Pelvic and abdominal ultrasonography is performed every 6–12 months from the age of 8–10 years to at least 40 years (recommended). Ovarian ultrasonography is performed annually between the ages of 8 and 20 years (to be considered)[101].
Supplementary information	Cancer types whose penetration rate is unknown, although they are thought to be associated with tumors: embryonal-type rhabdomyosarcoma of the cervix, pinealoblastoma, pituitary blastoma, intracranial sarcoma with DICER1-mt[102], ciliary medulloepithelioma, and nasal cartilage mesothelial hamartoma Genetic testing for *DICER1* is recommended for patients who have developed a related tumor[100]. Patients with pleuropulmonary blastoma type I are expected to have a favorable prognosis with surgical resection alone, but those with type II or III have a poor prognosis, even with chemotherapy. Pleuropulmonary blastoma type I may progress to type II or III, and its early detection is expected to improve prognosis[100, 103].

1

EPCAM

Disease	LYNCH SYNDROME 8; LYNCH8 (OMIM 613244) (GRJ Lynch syndrome)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.02%[1, 104]
Risk of cancer onset (penetration rate)	The risk is equivalent to that for *MSH2* (see 'Supplementary information')
Domestic clinical practice guidelines	Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition. Japanese Society for Cancer of the Colon and Rectum[31]
Clinical management recommended by domestic clinical practice guidelines	**Colon**: Colonoscopy is performed every 1–2 years starting at 20–25 years of age. **Uterus**: Endometrial histological diagnosis is performed every 1–2 years starting at 30–35 years of age. **Ovary**: Transvaginal US and serum CA125 measurement are performed (to be considered). Risk-reducing surgery (total hysterectomy or bilateral adnexectomy) is performed (to be considered). Total hysterectomy and bilateral adnexectomy are concurrently performed for patients requiring surgery for colorectal cancer (to be considered). **Stomach and duodenum**: Upper gastrointestinal endoscopy is performed every 1–3 years starting at 30–35 years of age (Eradication of *H. pylori* infection is performed, if present). **Renal pelvis/ureter** (to be considered for patients with an *MSH2* variant or a family history of urothelial carcinoma): Urinalysis (or urine cytology) is performed annually starting at 30–35 years of age. **Pancreas**: If the patient has a family history of pancreatic cancer, EUS or MRI/MRCP is started at 50 years of age (to be considered).
Clinical management recommended by international clinical practice guidelines Only items not described	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] Aspirin is orally administered to individuals with colorectal cancer risk (to be considered). Risk-reducing total hysterectomy can be considered for uterine body cancer. Risk-reducing drugs are administered for uterine body cancer and ovarian cancer (to be considered). If a first- or second-degree relative in the family line of GPV carriers has pancreatic cancer, surveillance for pancreatic cancer is started at 50 years of age or 10 years earlier than the onset age of the pancreatic cancer patient with the earliest onset in

in domestic practice guidelines are listed.	the family (to be considered).
Supplementary information	Deletion of the 3' region of *EPCAM*, which is located upstream of *MSH2*, significantly methylates the promoter region of *MSH2* and suppresses the transcription of the gene, causing Lynch syndrome. It has also been reported that the risk of developing uterine body cancer differs depending on the extent of the deletion of *EPCAM* (whether the deletion includes the *MSH2* region)[105]. Individuals carrying GPV in the homozygous or compound heterozygous state are known to present with congenital mismatch repair deficiency (CMMRD) syndrome[106].

1

1 # *FH*

2

Disease	HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER; HLRCC (OMIM 150800) (GRJ FH tumor predisposition syndrome)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	Renal cell carcinoma: 10–16%[107-109]
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Kidney Cancer. Version 3. 2024-Mar 11, 2024[47] **Renal cell carcinoma**: Abdominal MRI (prefereed) or CT, with and without IV contrast, is performed annually starting at 8–10 years of age.
Supplementary information	Synonyms include hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome, multiple cutaneous and uterine leiomyomatosis (MCL/MCUL), and Reed syndrome.

	Patients with renal cell carcinomas are provided with immediate surgical intervention without surveillance therapy due to their considerably high malignancy, such as metastasis from those with a small diameter[107, 110]. In principle, partial nephrectomy is not recommended as it often leads to local recurrence, but its indication should be carefully considered when it is performed for tumors with a small diameter[111]. Laparotomic nephrectomy should be actively performed, combined with lymph node dissection or wound lavage with large volumes of saline[111]. In chemotherapy, standard regimens for sporadic renal cancer are used, although their efficacy is limited[112]. In addition to renal cell carcinoma, systemic signs include cutaneous leiomyoma (≤50%) and uterine myoma (≤90% of women). However, due to the high incidence of uterine myoma in the general population and other factors, it is difficult to identify a family line before the development of renal cancer[110, 111].

1

FLCN

Disease	BIRT-HOGG-DUBE SYNDROME 1; BHD1 (OMIM 135150) (GRJ Birt-Hogg-Dubé syndrome)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	Renal cell carcinoma: 16–34%[113]
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Kidney Cancer. Version 3. 2024-Mar 11, 2024[47] **Renal cell carcinoma**: Abdominal MRI (preferred) or CT, with and without IV contrast, is performed every 3 years starting at 20 years of age.
Supplementary information	Renal cell carcinomas occurring in patients with BHD syndrome generally grow slowly, but they occur metachronously and multifocally. Thus, taking into account the balance between cancer control and preservation of renal function, kidney-sparing surgery is considered when the diameter of the largest tumor reaches 2 cm[113].

	In addition to renal cell carcinoma, reported signs include lung cysts (90%), spontaneous pneumothorax, and cutaneous fibrofolliculoma (20–29%), as well as salivary gland and thyroid tumors, although their incidence is low[113, 114].

1

GALNT12

Disease	COLORECTAL CANCER, SUSCEPTIBILITY TO, 1; CRCS1 (OMIM 608812)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	Unknown (see 'Supplementary information')
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] Individual management has not yet been established, and surveillance based on family history is considered.
Supplementary information	The detection rate of GPV in patients with colorectal cancer was reported to be 1.7–3.4%[115-117]. The frequency of GPV carriers, as well as the penetration of colorectal cancer, was reported as moderate[116], and the NCCN guidelines state that the risk (penetration rate) of developing colorectal cancer is 5–10% (estimated by an unknown source)[32].

1

GREM1

Disease	POLYPOSIS SYNDROME, HEREDITARY MIXED, 1; HMPS1 (OMIM 601228)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown (several families only: overseas)[118]
Risk of cancer onset (penetration rate)	Colorectal cancer: 11–20%[118]
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] **Colorectal cancer**: Starting at 25–30 years of age, colonoscopy is performed every 2–3 years for patients without polyps and every 1–2 years for patients with polyps. Surgery is considered if polyps become unmanageable by colonoscopy (to be considered).
Supplementary information	Some patients present with a clinical picture that overlaps with familial adenomatous polyposis (*APC*-related polyposis) and Lynch syndrome[119].

HOXB13

Disease	PROSTATE CANCER, HEREDITARY, 9; HPC9 (OMIM 610997)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.02–0.2%[1, 86], 0.1% [p.G84E, 1/1,401 persons (European-origin control population)][120]
Risk of cancer onset (penetration rate)	Unknown (see 'Supplementary information')
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	Philadelphia Prostate Cancer Consensus Conference 2019[121] It is recommended that this gene be included when performing genetic testing for patients meeting the criteria for hereditary prostate cancer. Its results should be taken into consideration when discussing early detection. Surveillance for prostate cancer is started 40 years or 10 years earlier than the age of the prostate cancer patient with the earliest onset in the family (to be considered).
Supplementary information	It has been reported that GPV in *HOXB13* is detected at a significantly high frequency among prostate cancer patients in the Japanese population (OR=4.73, $p<0.01$)[86]. It was reported that the p.G84E mutation was detected at a significantly higher frequency in the prostate cancer group than in the healthy control group (0.1% vs.

	1.4%, $p < 0.01$) and that the frequency was particularly high (3.1%) among families with early-onset familial prostate cancer[120]. Regarding GPV, pathological evaluation has not been established for p.G132E, which was reported in the Japanese population[86], or p.G135E, which was reported mainly in the Chinese population[122], and they are set as VUS in ClinVar (as of August 2024). A report stated that the p.G84E mutation in *HOX13* had no impact on prognosis and that its clinical utility in prostate cancer management had not been established[123].

1

1 ***MAX***

2

Disease	PHEOCHROMOCYTOMA, SUSCEPTIBILITY TO (OMIM 171300) (GRJ hereditary paraganglioma and pheochromocytoma syndrome)
Inheritance pattern	Autosomal dominant inheritance (possible paternal inheritance[124])
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	Pheochromocytoma and paraganglioma: unknown (see 'Supplementary information')
Domestic clinical practice guidelines	Clinical Practice Guidelines for Pheochromocytoma and Paraganglioma, 2018 Edition. The Japan Endocrine Society[125]
Clinical management recommended by domestic clinical practice guidelines	For cancer-free GPV carriers, surveillance is started 10 years earlier than the onset age of the affected family member with the earliest onset, with the following: medical examination, annual measurement of blood free (or urinary) metanephrine, annual CT or MRI, and triennial ^{123}I-MIBG scintigraphy (Note: This is only tentative, as it is not based on prospective studies.)
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	1. NCCN Guidelines®, Neuroendocrine and Adrenal Tumors. Version 1. 2024-Jun 20, 2024[126] Surveillance for pheochromocytoma and paraganglioma is started 10–15 years of age. Blood pressure is measured at every medical examination. Plasma free or 24-hour urinary metanephrine fraction is measured annually. Whole-body MRI is performed every 2–3 years. Abdominal MRI, MRI of the skull base to the neck, and chest CT are performed if whole-body MRI is not available (to be considered). 2. Personalized Management of Pheochromocytoma and Paraganglioma (2022)[127] If the patient has a history of pheochromocytoma, clinical evaluation and biochemical tests are performed annually, and abdominal-to-pelvic MRI is performed every 5 years.
Supplementary information	Tumors whose penetration rate is unknown, although their correlation with onset risk has been pointed out: pituitary adenomas There has been a report of a variant exhibiting high penetrance of pheochromocytomas (c.200C>A, p.A67D)[128].

	In the majority of cases, *MAX*-related hereditary pheochromocytoma and paraganglioma syndrome develops with pheochromocytomas (bilateral or multiple pheochromocytomas in many cases)[124]. Therefore, imaging tests specific to the adrenal glands are also considered[126]. 18F-FDOPA PET/CT has been reported to have high sensitivity in detecting *MAX*-related pheochromocytomas[129], although it is not approved in Japan.

MEN1

Disease	MULTIPLE ENDOCRINE NEOPLASIA, TYPE I; MEN1 (OMIM 131100) (GRJ multiple endocrine neoplasia type 1)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown (see 'Supplementary information')
Risk of cancer onset (penetration rate)	Pancreatic and gastrointestinal neuroendocrine tumor (NET): 58.6%[130] (>80% overseas)[131, 132], pituitary tumor: 49.6%[130] (30–60% overseas)[133], adrenocortical tumor: 20.1%[130], thymic/bronchial NET: 8.4%[130] (2–8% overseas)[134]
Domestic clinical practice guidelines	1. Guidebook for Management of Multiple Endocrine Neoplasia. Editorial Committee for Guidebook for Management of Multiple Endocrine Neoplasia (ed.)[135] 2. Clinical Practice Guidelines for Pancreatic and Gastrointestinal Neuroendocrine Tumors (NEN), 2019 Edition, 2nd Edition. Japan NeuroEndocrine Tumor Society (JNETS)/Creation Committee for Clinical Practice Guidelines for Pancreatic and Gastrointestinal Neuroendocrine Tumors, 2nd Edition[136]
Clinical management recommended by domestic clinical practice guidelines	**Pancreatic and gastrointestinal NET**: [Functional NET] Fasting glucose and insulin are measured annually starting at 5 years of age, and gastrin is measured annually starting at 20 years of age. CT/MRI is performed every 2–3 years starting at 10 years of age. [Non-functional NET] CT/MRI is performed annually. **Pituitary tumor**: Prolactin and insulin-like growth factor (IGF-1) are measured annually starting at 5 years of age, and MRI is performed every 3–5 years. **Adrenocortical tumor**: MRI/CT is performed every 2–3 years starting at 10 years of age. **Thymic/bronchial NET**: CT/MRI is performed every 2–3 years.
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are	1. Clinical Practice Guidelines for Multiple Endocrine Neoplasia Type 1 (MEN1) (2012)[137] **Pancreatic NET**: Gastrin, glucagon, VIP, pancreatic polypeptide, chromogranin A, insulin, and fasting blood glucose are measured annually. CT/MRI/abdominal ultrasonography is performed annually. **Gastric NET**: For patients with hypergastrinemia, upper gastrointestinal endoscopy is performed every 3 years. **Pituitary gland**: Prolactin and IGF-I are measured annually, and MRI is performed every 3–5 years. **Thymus and bronchus**: CT/MRI is performed every 1–2 years. **Adrenal glands**: CT/MRI is performed every 3 years. 2. Guidelines for Diagnosis and Therapy of MEN Type 1 and Type 2 (2001)[138] There are no additional recommended items.

listed.	
Supplementary information	Overseas, the GPV frequency was estimated to be approximately 1/30,000 persons[139]. The frequency was reported to be comparable in Japan, although the study targeted only specific regions[135]. Patients also develop primary hyperparathyroidism (≥90%). Many guidelines recommend starting surveillance at 5–8 years of age, but it has also been reported that the surveillance may be delayed until the mid-teens because of its low incidence rate before adolescence and its mostly asymptomatic nature even after the onset[137, 140].

1

MET

Disease	RENAL CELL CARCINOMA, PAPILLARY, 1; RCCP1 (OMIM 605074)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	Renal cancer: nearly 100% by 80 years of age[141, 142]
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines® Kidney Cancer. Version 3. 2024-Mar 11, 2024[47] Abdominal MRI (preferred) or CT, with and without IV contrast, is performed every 1–2 years starting at 30 years of age.
Supplementary information	The position, type, and other aspects of variants have been reported to be correlated with the onset risk[142].

MLH1

Disease	LYNCH SYNDROME 2; LYNCH2 (OMIM 609310) (GRJ Lynch syndrome)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.01–0.03%[1, 2], 1/1,946 persons (overseas)[143]
Risk of cancer onset (penetration rate)	Colorectal cancer: 41–46%[144, 145], uterine body cancer: 27–57%[144-146], ovarian cancer: 8–20%[144-147], renal pelvis and ureteral cancer: 0.2–5%[144, 145, 148], gastric cancer: 6–6.3%[144, 145], biliary tract cancer: 1.9–3.7%[144, 145], small intestinal cancer: 0.4%[144], pancreatic cancer: 3.9%[145], brain tumor: 1.0%[145]
Domestic clinical practice guidelines	Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition. Japanese Society for Cancer of the Colon and Rectum[31]
Clinical management recommended by domestic clinical practice guidelines	**Colon**: Colonoscopy is performed every 1–2 years starting at 20–25 years of age. **Uterus**: Endometrial histological diagnosis is performed every 1–2 years starting at 30–35 years of age. **Ovary**: Transvaginal US and serum CA125 measurement are performed (to be considered). Risk-reducing surgery (total hysterectomy or bilateral adnexectomy) is performed (to be considered). Total hysterectomy and bilateral adnexectomy are concurrently performed for patients requiring surgery for colorectal cancer (to be considered). **Stomach and duodenum**: Upper gastrointestinal endoscopy is performed every 1–3 years starting at 30–35 years of age (Eradication of *H. pylori* infection is performed, if present). **Renal pelvis/ureter** (to be considered for patients with an *MSH2* variant or a family history of urothelial carcinoma): Urinalysis (or urine cytology) is performed annually starting at 30–35 years of age. **Pancreas**: If the patient has a family history of pancreatic cancer, EUS or MRI/MRCP must start at 50 years of age (to be considered).
Clinical management recommended by international clinical practice guidelines Only items not described	1. NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] Aspirin is orally administered to individuals with colorectal cancer risk (to be considered). Prophylactic total hysterectomy is performed for uterine body cancer (to be considered). Risk-reducing drugs are administered for uterine body cancer and ovarian cancer (to be considered).

in domestic practice guidelines are listed.	If a first- or second-degree relative in the family line of GPV carriers has pancreatic cancer, surveillance for pancreatic cancer is started at 50 years of age or 10 years earlier than the onset age of the pancreatic cancer patient with the earliest onset in the family (to be considered). 2. Hereditary gastrointestinal cancers: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (2019)[149)] Surveillance with MRI or EUS can be considered if first-degree relatives have a family history of pancreatic cancer. 3. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer genetics group (UKCGG) (2020)[150)] There are no additional recommended items (see 'Supplementary information'). 4. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on colorectal cancer (2014)[151)] There are no additional recommended items (see 'Supplementary information').
Supplementary information	A decision on the selection of colorectal extension surgery or partial resection for colorectal cancer is made comprehensively in consideration of clinical background[150)]. Individuals carrying GPV in the homozygous or compound heterozygous state are known to present with congenital mismatch repair deficiency (CMMRD) syndrome[106)].

1

MSH2

Disease	LYNCH SYNDROME 1; LYNCH1 (OMIM 120435) (GRJ Lynch syndrome)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.02%[1, 2], 1/2,841 persons (overseas)[143]
Risk of cancer onset (penetration rate)	Colorectal cancer: 42.4–48%[144, 145], uterine body cancer: 21–52.7%[144, 145, 152], ovarian cancer: 16.9–24%[144, 145, 152], renal pelvis and ureteral cancer: 2.2–16.0%[144, 145, 148], gastric cancer: 0.2–4.1%[144, 145], biliary tract cancer: 0.02–1.7%[144, 145], small intestinal cancer: 1.1%[144], pancreatic cancer: 0.5%[145], brain tumor: 1.9%[145]
Domestic clinical practice guidelines	Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition. Japanese Society for Cancer of the Colon and Rectum[31]
Clinical management recommended by domestic clinical practice guidelines	**Colon**: Colonoscopy is performed every 1–2 years starting at 20–25 years of age. **Uterus**: Endometrial histological diagnosis is performed every 1–2 years starting at 30–35 years. **Ovary**: Transvaginal US and serum CA125 measurement are performed (to be considered). Risk-reducing surgery (total hysterectomy or bilateral adnexectomy) is performed (to be considered). Total hysterectomy and bilateral adnexectomy are concurrently performed for patients requiring surgery for colorectal cancer (to be considered). **Stomach and duodenum**: Upper gastrointestinal endoscopy is performed every 1–3 years starting at 30–35 years of age (Eradication of *H. pylori* infection is performed, if present). **Renal pelvis/ureter** (to be considered for patients with an *MSH2* variant or a family history of urothelial carcinoma): Urinalysis (or urine cytology) is performed annually starting at 30–35 years of age. **Pancreas**: If the patient has a family history of pancreatic cancer, EUS or MRI/MRCP is started at 50 years of age (to be considered).
Clinical management recommended by international clinical practice guidelines Only items not described in	1. NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] Aspirin is orally administered to individuals with colorectal cancer risk (to be considered). Prophylactic total hysterectomy is performed for uterine body cancer (to be considered). Risk-reducing drugs are administered for uterine body cancer and ovarian cancer (to be considered).

domestic practice guidelines are listed.	If a first- or second-degree relative in the family line of GPV carriers has pancreatic cancer, surveillance for pancreatic cancer is started at 50 years of age or 10 years earlier than the onset age of the pancreatic cancer patient with the earliest onset in the family (to be considered). 2. Hereditary gastrointestinal cancers: ESMO clinical practice guidelines for diagnosis, treatment and follow-up (2019)[149)] Surveillance with MRI or EUS can be considered if first-degree relatives have a family history of pancreatic cancer. 3. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer genetics group (UKCGG) (2020)[150)] There are no additional recommended items (see 'Supplementary information'). 4. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on colorectal cancer (2014)[151)] There are no additional recommended items (see 'Supplementary information').
Supplementary information	A decision on the selection of colorectal extension surgery or partial resection for colorectal cancer is made comprehensively in consideration of clinical background[150)]. Individuals carrying GPV in the homozygous or compound heterozygous state are known to present with congenital mismatch repair deficiency (CMMRD) syndrome[106)].

1

MSH3

Disease	FAMILIAL ADENOMATOUS POLYPOSIS 4; FAP4 (OMIM 617100)
Inheritance pattern	Autosomal recessive inheritance
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	Unknown (see 'Supplementary information')
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] **Colon**: Colonoscopy is started at 25–30 years of age. If the patient has polyps, colonoscopy is performed every 1–2 years, and surgery is also considered. If the patient has no polyps, colonoscopy is performed every 2–3 years.
Supplementary information	The detection frequency (in the homozygous state) in solid cancer-affected patients was reported to be 0.009% (overseas)[153]. In addition to polyposis coli, there have been reports of the development of duodenal polyposis, gastric cancer, and astrocytoma[154].

MSH6

Disease	LYNCH SYNDROME 5; LYNCH5 (OMIM 614350) (GRJ Lynch syndrome)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.04–0.06%[1, 2], 0.13% (1/758 persons) (overseas)[143]
Risk of cancer onset (penetration rate)	Colorectal cancer: 11.8–18%[144, 145, 155], uterine body cancer: 16–46.2%[144-146, 152, 156], ovarian cancer: 1–13.1%[144-146, 152], renal pelvis and ureteral cancer: 0.7–3.0%[144, 145], gastric cancer: 5.3%[145], pancreatic cancer: 1.4%[145], brain tumor: 1.4%[145]
Domestic clinical practice guidelines	Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition. Japanese Society for Cancer of the Colon and Rectum[31]
Clinical management recommended by domestic clinical practice guidelines	**Colon**: Colonoscopy is performed every 1–2 years starting at 30–35 years of age. **Uterus**: Endometrial histological diagnosis is performed every 1–2 years starting at 30–35 years of age. **Ovary**: Transvaginal US and serum CA125 measurement are performed (to be considered). Risk-reducing surgery (total hysterectomy or bilateral adnexectomy) is performed (to be considered). Total hysterectomy and bilateral adnexectomy are concurrently performed for patients requiring surgery for colorectal cancer (to be considered). **Stomach and duodenum**: Upper gastrointestinal endoscopy is performed every 1–3 years starting at 30–35 years of age (Eradication of *H. pylori* infection is performed, if present). **Renal pelvis/ureter** (to be considered for patients with an *MSH2* variant or a family history of urothelial carcinoma): Urinalysis (or urine cytology) is performed annually starting at 30–35 years of age. **Pancreas**: If the patient has a family history of pancreatic cancer, EUS or MRI/MRCP is started 50 years of age (to be considered).
Clinical management recommended by international clinical practice guidelines Only items not described in	1. NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] Aspirin is orally administered to individuals with colorectal cancer risk (to be considered). Prophylactic total hysterectomy is performed for uterine body cancer (to be considered). Risk-reducing drugs are administered for uterine body cancer and ovarian cancer (to be considered).

domestic practice guidelines are listed.	If a first- or second-degree relative in the family line of GPV carriers has pancreatic cancer, surveillance for pancreatic cancer is started 50 years of age or 10 years earlier than the onset age of the pancreatic cancer patient with the earliest onset in the family (to be considered). 2. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer genetics group (UKCGG) (2020)[150] There are no additional recommended items (see 'Supplementary information'). 3. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on colorectal cancer (2014)[151] There are no additional recommended items (see 'Supplementary information').
Supplementary information	A decision on the selection of colorectal extension surgery or partial resection for colorectal cancer is made comprehensively in consideration of clinical background[150]. Individuals carrying GPV in the homozygous or compound heterozygous state are known to present with congenital mismatch repair deficiency (CMMRD) syndrome[106].

1

MUTYH

Disease	FAMILIAL ADENOMATOUS POLYPOSIS 2; FAP2 (OMIM 608456) (GRJ *MUTYH* polyposis)
Inheritance pattern	Autosomal recessive inheritance
GPV frequency	Heterozygous 0.12%[2)]
Risk of cancer onset (penetration rate)	Colorectal cancer: unknown (see 'Supplementary information'), duodenal carcinoma: unknown (see 'Supplementary information')
Domestic clinical practice guidelines	Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition. Japanese Society for Cancer of the Colon and Rectum (ed.)[31)]
Clinical management recommended by domestic clinical practice guidelines	Lower gastrointestinal endoscopy is started at 25–30 years of age. Upper gastrointestinal endoscopy is started at 30–35 years of age. **Colorectal adenoma**: Management is provided in the same manner as that for attenuated FAP (AFAP).
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	1. NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32)] **Colorectal cancer**: Colonoscopy is started at 25–30 years of age. If the adenoma can be managed by endoscopy, colonoscopy, and polypectomy are performed every 1–2 years. If the adenoma cannot be managed by endoscopy, total colectomy and ileorectal anastomosis (IRA) are performed, followed by rectal endoscopy every 6–12 months according to the status of polyps. If rectal polyposis cannot be managed by polypectomy, total colorectal resection and ileal pouch anal anastomosis (IPAA) are performed. **Gastric/duodenal carcinoma**: Management may be started at an early age if the patient has a family history of duodenal adenoma/carcinoma. Surveillance interval is determined based on the Spigelman score if the patient has duodenal polyps and based on size and histological type if the patient has gastric polyps. Referral to a specialized medical institution or surgical resection is also considered. **Extra-gastrointestinal malignant tumor**: Physical examination is performed annually.

	2. European Society of Gastrointestinal Endoscopy (ESGE) guideline[157] **Colonoscopy**: Colonoscopy is performed at intervals of 1–2 years starting at 18 years of age. All polyps with a size of >5 mm are resected. **Upper gastrointestinal endoscopy**: Duodenal papillae are evaluated based on the Spigelman score starting at 35 years of age. Adenomas with a Spigelman score of >10 are endoscopically resected (to be considered). 3. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG)[150] **Colonoscopy**: Colonoscopy is performed annually starting at 18–20 years of age. **Upper gastrointestinal endoscopy**: Upper gastrointestinal endoscopy is started at 35 years of age, with intervals determined based on the Spigelman score (to be considered). 4. American Society for Gastrointestinal Endoscopy[158] **Colonoscopy**: Colonoscopy is performed every 1–2 years starting at 18–20 years of age. **Upper gastrointestinal endoscopy**: Upper gastrointestinal endoscopy is performed 30–35 years of age or before colorectal resection (with intervals determined based on Spigelman stage, grade, etc.).
Supplementary information	Among individuals carrying GPV in both alleles of *MUTYH*, the risk of developing colorectal cancer by 60 years of age was estimated to be 42.89%[159], and the risk of developing duodenal carcinoma by 75 years of age was estimated to be 4%[160]. Among those carrying no GPV in *APC* despite being clinically diagnosed with familial adenomatous polyposis (*APC*-related polyposis), it was reported that 7% of patients with 20–99 colorectal adenomas, as well as 4% of patients with 10–19 colorectal adenomas, carried GPV in both alleles of *MUTYH*[161]. It was reported that no polyposis was found in patients carrying the splicing variant frequently detected in Japan (c.892-2A>G, rs77542170), even in the homozygous state[2].

1

NF1

Disease	NEUROFIBROMATOSIS, TYPE I; NF1 (OMIM 162200) (GRJ neurofibromatosis type 1)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.05%[162]
Risk of cancer onset (penetration rate)	Neurofibroma (skin: 95%[163], nerve: 20%[163], diffuse: 10%[163]), malignant peripheral nerve sheath tumor: 2%[163], optic glioma: 7–8%[163], gastrointestinal stromal tumor (GIST): unknown (see 'Supplementary information'), breast cancer: unknown
Domestic clinical practice guidelines	1. Clinical Practice Guidelines for Neurofibromatosis Type 1 (von Recklinghausen disease), 2018 Edition. Revision Committee for Clinical Practice Guidelines for Neurofibromatosis Type 1 (ed.)[163] 2. Clinical Practice Guidelines for Brain Tumor: Pediatric Brain Tumor, 2021 Edition. Japan Society for Neuro-Oncology (ed.)[164] 3. Clinical Practice Guidelines for Plexiform Neurofibroma-Malignant Peripheral Nerve Sheath Tumor. Creation Committee for Clinical Practice Guidelines for Plexiform Neurofibroma-Malignant Peripheral Nerve Sheath Tumor (ed.)[165]
Clinical management recommended by domestic clinical practice guidelines	Periodic follow-up is performed every 6 months to 1 year in children and every one to several years in adults. **Children aged <7 years**: Attention should be paid to the presence or absence of visual impairment associated with complications of optic glioma. **Pheochromocytoma**: Referral to a urologist is made if the patient presents with hypertension or tumors in the adrenal glands. **Gastrointestinal stromal tumor**: Referral to a gastroenterological surgery specialist is made if the patient presents with melena, abdominal pain, or other symptoms. Surveillance for plexiform neurofibroma is performed with whole-body MRI (conditionally recommended).
Clinical management recommended by international clinical practice guidelines Only items not described in domestic	1. Health Supervision for Children With Neurofibromatosis Type 1 (2019)[166] 2. NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3. 2024-February 12, 2024[38] **Breast cancer**: Mammography is performed annually starting at 30 years of age, and breast MRI, with and without contrast, is consideredannually starting at 30–50 years of age. **Malignant peripheral nerve sheath tumor/GIST**: Referral to a physician specialized in NF1 is made for evaluation and management.

practice guidelines are listed.	
Supplementary information	The GPV frequency was estimated to be approximately 1/3,000 persons[167]. Gastrointestinal stromal tumor (GIST): Although the risk has been reported to be 5–25%[163, 168], it was also reported to be unknown. A family analysis showed that 50% of NF1 cases were caused by de novo mutations[169].

1

NF2

Disease	SCHWANNOMATOSIS, VESTIBULAR; SWNV (OMIM 101000) (GRJ neurofibroma type 2)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	1/28,000 persons[170]
Risk of cancer onset (penetration rate)	Bilateral acoustic neurilemoma: 90–95%[171, 172], spinal cord tumor (intraspinal and extraspinal tumors): 63–90%[171], neurilemoma of other cranial nerves: 24–51%[171], intracranial meningioma: 45–77%[173], subcutaneous tumor: 43–48%[174]
Domestic clinical practice guidelines	Treatment Guidelines for Neurofibromatosis Type 2 (Revised October 2016), "Research Group on Neurocutaneous Syndromes" (ed.)[175]
Clinical management recommended by domestic clinical practice guidelines	No starting age has been specified. **Acoustic neurilemoma**: Brain MRI is performed. **Spinal neurilemoma**: Spinal cord MRI is performed. **Trigeminal neurilemoma**: Brain MRI is performed (every 6 months if the patient has a tumor). **Meningioma**: MRI is performed (every 6 months if the patient has a tumor).
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	Updated protocol for genetic testing, screening and clinical management of individuals at risk of NF2-related Schwannomatosis (2023)[176] There are no additional recommended items.
Supplementary information	—

NTHL1

Disease	FAMILIAL ADENOMATOUS POLYPOSIS 3; FAP3 (OMIM 616415) (GRJ *NTHL1* tumor syndrome)
Inheritance pattern	Autosomal recessive inheritance[177]
GPV frequency	1/114,770 persons (Europe)[178]
Risk of cancer onset (penetration rate)	Colorectal cancer: 47%[179]
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	1. NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] **Colon**: Starting at 25–30 years of age, colonoscopy is performed every 2–3 years for patients with no lesions and every 1–2 years for patients with polyps. Surgery is considered if polyps are difficult to remove endoscopically (limited strength of evidence). **Duodenum**: Baseline duodenoscopy (including adequate observation of the Vater papillae) is started at 30–35 years of age. Thereafter, surveillance is performed in the same manner as that for familial adenomatous polyposis (*APC*-related polyposis). **Endometrium**: Postmenopausal transvaginal ultrasonography may be considered at the discretion of the physician. 2. Hereditary gastrointestinal cancers: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2019)[149] Along with periodic surveillance with colonoscopy, the same approach is taken as that for *MUTYH* polyposis.
Supplementary information	Cancer types whose penetration rate is unknown, although their correlation with onset risk has been pointed out: breast cancer, uterine body cancer, and duodenal carcinoma.

PALB2

Disease	BREAST-OVARIAN CANCER, FAMILIAL, SUSCEPTIBILITY TO, 5; BROVCA5 (OMIM 620442)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.05%[1], 0.12% (overseas)[49]
Risk of cancer onset (penetration rate)	Breast cancer: 44% (<80 years of age)[180], male breast cancer: 0.9%[181], ovarian cancer: 5% (<80 years of age)[181], pancreatic cancer: 2–3% (<80 years of age)[181]
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3. 2024-February 12, 2024[38] **Breast cancer**: Mammography is performed annually starting at 30 years of age. Breast MRI, with and without contrast, is performed annually starting at 30 years of age. Risk-reducing mastectomy is performed (to be considered). Male breast cancer is managed in the same manner as that for *BRCA1* (to be considered). **Ovarian cancer**: Risk-reducing salpingo-oophorectomy is started at 45–50 years of age (to be considered). **Pancreatic cancer**: For GPV carriers who have at least one first- or second-degree relative with a family history of pancreatic cancer, surveillance (contrast-enhanced MRI/MRCP and/or EUS) is performed annually starting 50 years (or 10 years earlier than the onset age of the affected family member with the earliest onset) (to be considered).

Supplementary information	—

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PMS2

Disease	LYNCH SYNDROME 4; LYNCH4 (OMIM 614337) (GRJ Lynch syndrome)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.04–0.05%[1, 2], 1/714 persons (overseas)[143]
Risk of cancer onset (penetration rate)	Colorectal cancer: 3.4–13.0%[152, 155], uterine body cancer: 12.8–26.4%[145, 152, 182, 183], ovarian cancer: 3.0%[152], renal pelvis and ureteral cancer: 3.7%[152]
Domestic clinical practice guidelines	Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition. Japanese Society for Cancer of the Colon and Rectum[31]
Clinical management recommended by domestic clinical practice guidelines	**Colon**: Colonoscopy is performed every 1–3 years starting at 30–35 years of age. **Uterus**: Endometrial histological diagnosis is performed every 1–2 years starting at 30–35 years of age. **Ovary**: Transvaginal US and serum CA125 measurement are performed (to be considered). Risk-reducing surgery (total hysterectomy or bilateral adnexectomy) is performed (to be considered). Total hysterectomy and bilateral adnexectomy are concurrently performed for patients requiring surgery for colorectal cancer (to be considered). **Stomach and duodenum**: Upper gastrointestinal endoscopy is performed every 1–3 years starting at 30–35 years of age (Eradication of *H. pylori* infection is performed, if present). **Renal pelvis/ureter** (to be considered for patients with an *MSH2* variant or a family history of urothelial carcinoma): Urinalysis (or urine cytology) is performed annually starting at 30–35 years of age. **Pancreas:** If the patient has a family history of pancreatic cancer, EUS or MRI/MRCP is started 50 years of age (to be considered).
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	1. NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] Aspirin is orally administered to individuals with colorectal cancer risk (to be considered). Prophylactic total hysterectomy is performed for uterine body cancer (to be considered). Risk-reducing drugs are administered for uterine body cancer and ovarian cancer (to be considered). 2. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great

	Britain and Ireland (ACPGBI)/United Kingdom Cancer genetics group (UKCGG) (2020)[150] There are no additional recommended items. 3. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on colorectal cancer (2014)[151] There are no additional recommended items.
Supplementary information	Individuals carrying GPV in the homozygous or compound heterozygous state are known to present with congenital mismatch repair deficiency (CMMRD) syndrome[106].

1

POLD1

Disease	COLORECTAL CANCER, SUSCEPTIBILITY TO, 10; CRCS10 (OMIM 612591)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	(Limited evidence is available.) Colorectal cancer: 90% in men and 82%[184] or 50%[185] in women (<70 years of age), uterine body cancer: 75% (<70 years of age)[185], breast cancer: 20% (<60 years of age)[185]
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] (Limited evidence is available.) Colonoscopy is started at 25–30 years of age or 2–5 years earlier than the onset age of a close relative diagnosed before 25 years of age, if the patient has such a relative. Colonoscopy is performed every 2–3 years if the patient has no polyps and every 1–2 years if the patient has polyps. Surgery is considered if polyps become unmanageable by endoscopic therapy.
Supplementary information	**Extracolonic lesion**: There have been reports of an increased risk of brain tumor, in addition to the aforementioned uterine body cancer and breast cancer[184, 186, 187]. **Association with tumor mutation burden (TMB)**: It has been reported that alterations in the exonuclease domain affect DNA binding and activity, leading to a number of somatic mutations (TMB-high) and contributing to tumorigenesis[187, 188].

	In Reference #185, *POLD1* was identified in 27 of the 132 patients examined.

1

POLE

Disease	COLORECTAL CANCER, SUSCEPTIBILITY TO, 12; CRCS12 (OMIM 615083)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	(Limited evidence is available.) Colorectal cancer: 28% in men and 21%[184] or 90%[185] in women (<70 years of age), uterine body cancer: 25% (<70 years of age)[185], breast cancer: 20% (<60 years of age)[185]
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] (Limited evidence is available.) Starting 25–30 years of age, colonoscopy is performed every 2–3 years if the patient has no polyps and every 1–2 years if the patient has polyps. Surgery is considered if polyps become unmanageable by endoscopic therapy.
Supplementary information	**Extracolonic lesion**: There have been reports of an increased risk of ovarian cancer, brain tumor, pancreatic cancer, and melanoma, in addition to aforementioned uterine body cancer and breast cancer[184, 189-193]. **Association with tumor mutation burden (TMB)**: It has been reported that alterations in the exonuclease domain affect DNA binding and activity, leading to a

	number of somatic mutations (TMB-high) and contributing to tumorigenesis[187, 188]. In Reference #185, *POLE* was identified in 105 of the 132 patients examined.

1

PTEN

Disease	COWDEN SYNDROME 1; CWS1 (OMIM 158350) (GRJ *PTEN* hamartoma tumor syndrome)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.02%[1)]
Risk of cancer onset (penetration rate)	Breast cancer (women): 85% (71.4–99.1%)[194)], epithelial thyroid cancer: 35.2% (19.7–50.7%)[194)], uterine body cancer: 28.2% (17.1–39.3%)[194)], colorectal cancer: 9.0% (3.8–14.1%)[194)], renal cancer: 33.6% (10.4–56.9%)[194)], malignant melanoma: 6% (1.6–9.4%)[194)]
Domestic clinical practice guidelines	Clinical Practice Guidelines for Cowden Syndrome/*PTEN* Hamartoma Tumor Syndrome in Children and Adults (2020 Edition). Journal of Hereditary Tumors. 2020[195)]
Clinical management recommended by domestic clinical practice guidelines	**Breast cancer**: Breast self-examination is started at 18 years of age. Medical interview and palpation are performed every 6–12 months starting 25 years of age or 5–10 years earlier than the onset age of the breast cancer patient with the earliest onset in the family, whichever is earlier. Mammography or gadolinium-contrast-enhanced MRI is performed annually starting at 30 years of age or 5–10 years earlier than the onset age of the breast cancer patient with the earliest onset in the family. **Thyroid cancer**: Thyroid ultrasonography is performed from the time of diagnosis, including childhood. **Uterine body cancer**: Endometrial transvaginal ultrasonography or biopsy is performed annually starting at 30 years of age. **Colorectal cancer**: Complete colonoscopy is performed every 5 years starting at 35 years of age. (If close relatives have developed colorectal cancer by 40 years of age, complete colonoscopy is performed at shorter intervals depending on the presence of symptoms and polyps, starting 5–10 years earlier than the onset age of the colorectal cancer patient with the earliest onset in the family.) **Renal cell carcinoma**: Renal ultrasonography is performed annually starting at 40 years of age.
Clinical management recommended by international clinical practice guidelines	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3. 2024-February 12, 2024[38)] There are no additional recommended items.

Only items not described in domestic practice guidelines are listed.	
Supplementary information	Some patients with partial deletions of 10q22-23 involving *PTEN* or *BMPR1A* have clinical features of both Cowden syndrome/*PTEN* hamartoma tumor syndrome and juvenile polyposis syndrome and present with a clinical picture of severe early-onset polyposis[55].

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RAD51C

Disease	BREAST-OVARIAN CANCER, FAMILIAL, SUSCEPTIBILITY TO, 3; BROVCA3 (OMIM 613399)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.04%[1], 0.05% (overseas)[36]
Risk of cancer onset (penetration rate)	Breast cancer: 17–30%[36, 37, 49], ovarian cancer: 10–15%[68, 196, 197]
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3. 2024-February 12, 2024[38] **Breast cancer**: Mammography is performed annually starting at 40 years of age. Breast MRI with and without contrast is performed annually starting at 40 years of age (to be considered). **Ovarian cancer**: Risk-reducing salpingo-oophorectomy is started at 45–50 years of age.
Supplementary information	—

RAD51D

Disease	BREAST-OVARIAN CANCER, FAMILIAL, SUSCEPTIBILITY TO, 4; BROVCA4 (OMIM 614291)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.32%[1], 0.05% (overseas)[36]
Risk of cancer onset (penetration rate)	Breast cancer: 17–30%[36, 37, 49], ovarian cancer: 10–20%[68, 196, 197]
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3. 2024-February 12, 2024[38] **Breast cancer**: Mammography is performed annually starting at 40 years of age. Breast MRI with and without contrast is performed annually starting at 40 years of age (to be considered). **Ovarian cancer**: Risk-reducing salpingo-oophorectomy is started at 45–50 years of age.
Supplementary information	—

RB1

Disease	RETINOBLASTOMA; RB1 (OMIM 180200) (GRJ retinoblastoma)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown (see 'Supplementary information')
Risk of cancer onset (penetration rate)	Retinoblastoma: The penetration rate varies depending on the variant type. (Patients with a nonsense or frameshift variant have nearly complete penetrance. A low penetration rate has been observed in some patients with a missense variant, in-frame variant, variant of certain splicing sites, variant of promoters, and other variant types[198, 199]. It has been reported that a low penetration rate may also be found in mosaic cases[200].)
Domestic clinical practice guidelines	Clinical Practice Guidelines for Pediatric Cancer, 2016 Edition. The Japanese Society of Pediatric Hematology/Oncology[201]
Clinical management recommended by domestic clinical practice guidelines	The usefulness of continued periodic testing for secondary cancers has not been established.
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	1. Retinoblastoma and Neuroblastoma Predisposition and Surveillance (2017)[202] 2. Screening Children at Risk for Retinoblastoma: Consensus Report from the American Association of Ophthalmic Oncologists and Pathologists (2018)[203] **Eye**: Fundus examination is performed (for retinoblastoma-free individuals) at the following intervals: Birth to 8 weeks of age: every 2–4 weeks (without sedation), 8 weeks to 12 months of age: every month (under general anesthesia), 12–24 months of age: every 2 months (under general anesthesia), 24–36 months of age: every 3 months (under general anesthesia), 36–48 months of age: every 4 months (under general anesthesia), 48–60 months of age: every 6 months (under general anesthesia), 5–7 years of age: every 6 months (without sedation) **Trilateral retinoblastoma**: Brain MRI is performed at the time of diagnosis of retinoblastoma. (Some facilities recommend that brain MRI be performed every 6 months until 5 years of age.) **Secondary cancer**: Education on the risk of secondary cancers is provided, and close attention should be paid to new signs and symptoms. Skin examination is performed by a pediatrician during outpatient visits, and medical examination is performed annually by the primary care physician or a dermatologist after the age of 18 years, keeping melanoma in mind. Annual whole-body MRI may be considered after 8 years of age, although there has been no consensus.

Supplementary information	Based on the national data on retinoblastoma between 1983 and 2014, the frequency of GPV carriers was calculated to be 1/38,000–41,000 persons, given that the mean incidence was 1/16,823 births and that 100% of bilateral cases and 15–20% of unilateral cases were hereditary[204]. **Unaffected individuals with a family history (if the genetic testing results of the proband are unknown or if genetic testing has not been performed)**: It is recommended that fundus examination be performed every 3–4 months from birth to 3–4 years of age and every 6 months up to 5–6 years of age (it should be performed under general anesthesia, if possible).

1

RET

Disease	MULTIPLE ENDOCRINE NEOPLASIA, TYPE IIA; MEN2A (OMIM 171400) and MULTIPLE ENDOCRINE NEOPLASIA, TYPE IIB; MEN2B (OMIM 162300) (GRJ multiple endocrine neoplasia type 2)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown (see 'Supplementary information')
Risk of cancer onset (penetration rate)	Medullary thyroid carcinoma: nearly 100%[205], pheochromocytoma: 39.8%[206]
Domestic clinical practice guidelines	Guidebook for Management of Multiple Endocrine Neoplasia. Editorial Committee for Guidebook for Management of Multiple Endocrine Neoplasia (ed.) (2013)[135]
Clinical management recommended by domestic clinical practice guidelines	**Medullary thyroid carcinoma**: Cervical ultrasonography and blood calcitonin measurement are performed annually from childhood. (Prophylactic thyroidectomy is not approved in Japan.) **Pheochromocytoma**: CT/MRI and measurements of blood and 24-hour urinary metanephrine are performed annually (or every 3–5 years for patients with no abnormalities) starting 8 years of age if the patient carries a codon C634 variant and starting around the age of 20 years if the patient carries other mutations.
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	1. NCCN Guidelines®, Thyroid Carcinoma. Version 2. 2024[207] Calcitonin measurement, CEA measurement, ultrasonography, and CT are performed for patients with MEN2B. Prophylactic thyroidectomy with lymph node dissection is performed within the first year of birth. Among patients with MEN2A/FMTC, those with p.M918T are at the highest risk, and those with a codon C634 or A883 variant are at high risk, while others are considered to have a moderate risk. For high-risk patients, it is desirable that prophylactic thyroidectomy with lymph node dissection be performed at a young age. For moderate-risk patients, surgery may be delayed if no abnormalities are observed in annual measurements of blood calcitonin levels and annual ultrasonography. 2. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma (2015)[208] In adults, calcitonin levels are measured annually if they are within the normal range. Prophylactic thyroidectomy is performed if elevated calcitonin levels (>150 pg/mL) are observed. In children, prophylactic thyroidectomy is performed within the first year of birth if they are at the highest risk according to the ATA (American Thyroid

	Association risk categories for aggressive medullary thyroid carcinoma). For high-risk patients, surveillance is started at 3 years of age, and surgery is performed by 5 years of age, depending on the calcitonin level. For moderate-risk patients, surveillance is started at 5 years of age. The timing of prophylactic thyroidectomy is determined based on the elevation of calcitonin levels. If parents are concerned about long-term surveillance, the timing of surgery is decided by the attending surgeon/pediatrician in consultation with the parents. 3. Guidelines for Diagnosis and Therapy of MEN Type 1 and Type 2 (2001)[138] Blood metanephrine measurement, 24-hour urinary catecholamine or metanephrine measurement, CT, and MRI are performed.
Supplementary information	The frequency of MEN2 patients was estimated to be 1/45,000–270,000 persons in Japan[135] and 1/30,000 persons overseas[209]. A Denmark study reported that the annual incidence of MEN2A was 1/35,714 births[210]. The relevant gene needs to be evaluated for each variant (genotype-phenotype correlation). Primary hyperparathyroidism also occurs (20–30%)[138]. Serum calcium levels and parathyroid hormone levels are measured (starting at 8 years of age if the patient carries a codon C634 variant and starting at 20 years of age if the patient carries other mutations).

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RNF43

Disease	SESSILE SERRATED POLYPOSIS CANCER SYNDROME; SSPCS (OMIM 617108)
Inheritance pattern	Autosomal dominant inheritance[201]
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	Unknown (see 'Supplementary information')
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] Patients with serrated polyposis are managed according to the recommended management strategies for serrated polyposis syndrome. (Limited evidence is available.) **Colonoscopy**: Colonoscopy is performed every 1–3 years (depending on the number and size of polyps) after removing all polyps with a size of ≥5 mm. Referral to surgery is made if colonoscopic resection and/or surveillance is inadequate (to be considered).
Supplementary information	The NCCN guidelines state that the risk of developing colorectal cancer in *RNF43* GPV carriers is unknown ('insufficient data to define')[32].

RPS20

Disease	Not applicable
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown[201]
Risk of cancer onset (penetration rate)	Unknown
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] (No sufficient evidence is available.) Colonoscopy is performed every 5 years starting at 20 years of age. If the patient has undergone hematopoietic cell transplantation before 20 years of age, colonoscopy is started one year after the transplantation.)
Supplementary information	The NCCN guidelines state that no sufficient data is available on the absolute risk of colorectal cancer[32]. It was reported that GPV in *RPS20* was identified in children with Diamond-Blackfan anemia (DBA). It was reported that patients with *RPS20*-related hereditary non-polyposis colorectal cancer show no microsatellite instability or susceptibility to malignant tumors other than colorectal cancer[211].

SDHA

Disease	PHEOCHROMOCYTOMA/PARAGANGLIOMA SYNDROME 5; PPGL5 (OMIM 614165) (GRJ hereditary paraganglioma and pheochromocytoma syndrome)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	Pheochromocytoma and paraganglioma: 1.7%[212]
Domestic clinical practice guidelines	Clinical Practice Guidelines for Pheochromocytoma and Paraganglioma, 2018 Edition. The Japan Endocrine Society[125]
Clinical management recommended by domestic clinical practice guidelines	For cancer-free GPV carriers, surveillance is started 10 years earlier than the onset age of the affected family member with the earliest onset, with the following: medical examination, annual measurement of blood free (or urinary) metanephrine, annual CT or MRI, and triennial ^{123}I-MIBG scintigraphy (Note: This is only tentative, as it is not based on prospective studies.)
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	1. UK recommendations for SDHA germline genetic testing and surveillance in clinical practice[213] For patients with a medical or family history of pheochromocytoma and paraganglioma or other *SDHA*-related tumors (see 'Supplementary information'): Surveillance with blood pressure measurement, medical interview for related symptoms, and measurement of plasma free metanephrine fraction is performed annually starting at 10 years of age. Imaging examination from the neck to pelvis is performed every 3–5 years starting at 15 years of age (MRI is preferred). 2. NCCN Guidelines®, Neuroendocrine and Adrenal Tumors. Version 1. 2024-Jun 20, 2024[126] Surveillance for pheochromocytoma and paraganglioma is started at 10–15 years of age. Blood pressure is measured at every medical examination. Plasma free or 24-hour urinary metanephrine fraction is measured annually. Whole-body MRI is performed every 2–3 years. Abdominal MRI, MRI of the skull base to the neck, and chest CT are considered if whole-body MRI is not available. Surveillance intervals may be changed, given the low penetrance rate. 3. International consensus on initial screening and follow-up of asymptomatic SDHx

	mutation carriers (2021)[214] Surveillance is started at 10–15 years of age. For patients aged ≥18 years, initial surveillance is performed with blood pressure measurement, medical interview for PPGL-related symptoms, biochemical tests (plasma free metanephrine and normetanephrine are preferred to urine biochemistry), MRI (head-and-neck and abdominal-to-pelvic MRI), and PET-CT. In subsequent surveillances, blood pressure measurement, medical interview for related symptoms, and biochemical tests (plasma free metanephrine fraction is preferred to urinary fraction) are performed annually, and MRI (head-and-neck and chest-to-pelvic MRI) is performed every 2–3 years. The methods and intervals of surveillance differ for pediatric patients, for which the guidelines above should be referred to. No additional imaging tests are recommended for renal cell carcinoma or GIST, and patients should be examined simultaneously with imaging tests for PPGL.
Supplementary information	Cancer types whose penetration rate is unknown although their correlation with onset risk has been pointed out: GIST, renal cell carcinoma, pituitary adenoma, and neuroblastoma. Surveillance is not recommended for patients with no medical or family history of pheochromocytoma and paraganglioma or other *SDHA*-related tumors (GIST, renal cell carcinoma, pituitary adenoma, and neuroblastoma)[214].

1

SDHAF2

Disease	PHEOCHROMOCYTOMA/PARAGANGLIOMA SYNDROME 2; PPGL2 (OMIM 601650) (GRJ hereditary paraganglioma and pheochromocytoma syndrome)
Inheritance pattern	Autosomal dominant inheritance (paternal inheritance[215, 216])
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	Pheochromocytoma and paraganglioma: unknown (see 'Supplementary information')
Domestic clinical practice guidelines	Clinical Practice Guidelines for Pheochromocytoma and Paraganglioma, 2018 Edition. The Japan Endocrine Society[125]
Clinical management recommended by domestic clinical practice guidelines	For cancer-free GPV carriers, surveillance is started 10 years earlier than the onset age of the affected family member with the earliest onset, with the following: medical examination, annual measurement of blood free (or urinary) metanephrine, annual CT or MRI, and triennial ^{123}I-MIBG scintigraphy (Note: This is only tentative, as it is not based on prospective studies.)
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	1. NCCN Guidelines®, Neuroendocrine and Adrenal Tumors. Version 1. 2024-Jun 20, 2024[126] Surveillance for pheochromocytoma and paraganglioma is started at 10–15 years of age. Blood pressure is measured at every medical examination. Plasma free or 24-hour urinary metanephrine fraction is measured annually. Whole-body MRI is performed every 2–3 years. Abdominal MRI, MRI of the skull base to the neck, and chest CT are performed if whole-body MRI is not available (to be considered). 2. Personalized Management of Pheochromocytoma and Paraganglioma (2022)[127] If the patient has a history of pheochromocytoma, clinical evaluation and biochemical tests are performed annually, and abdominal-to-pelvic MRI is performed every 5 years.
Supplementary information	*SDHAF2*-related hereditary pheochromocytoma and paraganglioma syndrome often develops with head and neck paragangliomas[215, 217, 218]. Therefore, imaging tests specific to the head and neck region are also considered[126].

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1 ## *SDHB*

2

Disease	PHEOCHROMOCYTOMA/PARAGANGLIOMA SYNDROME 4; PPGL4 (OMIM 115310) (GRJ hereditary paraganglioma and pheochromocytoma syndrome)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	Pheochromocytoma and paraganglioma: 22%[212] (see 'Supplementary information'), renal cell carcinoma: 4.7% (<60 years of age)[219]
Domestic clinical practice guidelines	Clinical Practice Guidelines for Pheochromocytoma and Paraganglioma, 2018 Edition. The Japan Endocrine Society[125]
Clinical management recommended by domestic clinical practice guidelines	For cancer-free GPV carriers, surveillance is started 10 years earlier than the onset age of the affected family member with the earliest onset, with the following: medical examination, annual measurement of blood free (or urinary) metanephrine, annual CT or MRI, and triennial ^{123}I-MIBG scintigraphy (Note: This is only tentative, as it is not based on prospective studies.)
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	1. NCCN Guidelines®, Neuroendocrine and Adrenal Tumors. Version 1. 2024-Jun 20, 2024[126] Surveillance for pheochromocytoma and paraganglioma is started at 6–10 years of age. Blood pressure is measured at every medical examination. Plasma free or 24-hour urinary metanephrine fraction is measured annually. Whole-body MRI is performed every 2–3 years. Abdominal MRI, MRI of the skull base to the neck, and chest CT are performed if whole-body MRI is not available (to be considered). 2. International consensus on initial screening and follow-up of asymptomatic SDHx mutation carriers (2021)[214] Surveillance is started at 6–10 years of age. For adult patients aged ≥18 years, initial surveillance is performed with blood pressure measurement, medical interview for PPGL-related symptoms, biochemical tests (plasma free metanephrine and normetanephrine are preferred to urine biochemistry), MRI (head-and-neck and abdominal-to-pelvic MRI), and PET-CT. In subsequent surveillances, blood pressure measurement, medical interview for related symptoms, and biochemical tests (plasma free metanephrine fraction is preferred to urinary fraction) are performed annually, and MRI (head-and-neck and chest-to-pelvic MRI) is

	performed every 2–3 years. The methods and intervals of surveillance differ for pediatric patients, for which the guidelines above should be referred to. No additional imaging tests are recommended for renal cell carcinoma or GIST, and patients should be examined simultaneously with imaging tests for PPGL.
Supplementary information	Cancer types whose penetration rate is unknown although their correlation with onset risk has been pointed out: GIST and pituitary adenomas *SDHB*-related hereditary pheochromocytoma and paraganglioma are more likely to develop with paragangliomas than with pheochromocytomas, and the risk of distant metastasis is high at 35–75%[127]. Studies on surveillance for individuals carrying GPV in *SDHx* (*SDHB*, *SDHD*, and *SDHC*)[220-222] have reported that the early diagnosis of *SDHB*-related hereditary pheochromocytoma and paraganglioma particularly reduces the risk of distant metastasis and improves survival rates[220].

1

SDHC

Disease	PHEOCHROMOCYTOMA/PARAGANGLIOMA SYNDROME 3; PPGL3 (OMIM 605373) (GRJ hereditary paraganglioma and pheochromocytoma syndrome)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	Pheochromocytoma and paraganglioma: 8.3%[212] (see 'Supplementary information')
Domestic clinical practice guidelines	Clinical Practice Guidelines for Pheochromocytoma and Paraganglioma, 2018 Edition. The Japan Endocrine Society[125]
Clinical management recommended by domestic clinical practice guidelines	For cancer-free GPV carriers, surveillance is started 10 years earlier than the onset age of the affected family member with the earliest onset, with the following: medical examination, annual measurement of blood free (or urinary) metanephrine, annual CT or MRI, and triennial ^{123}I-MIBG scintigraphy (Note: This is only tentative, as it is not based on prospective studies.)
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	1. NCCN Guidelines®, Neuroendocrine and Adrenal Tumors. Version 1. 2024-Jun 20, 2024[126] Surveillance for pheochromocytoma and paraganglioma is started at 10–15 years of age. Blood pressure is measured at every medical examination. Plasma free or 24-hour urinary metanephrine fraction is measured annually. Whole-body MRI is performed every 2–3 years. Abdominal MRI, MRI of the skull base to the neck, and chest CT are performed if whole-body MRI is not available (to be considered). 2. International consensus on initial screening and follow-up of asymptomatic SDHx mutation carriers (2021)[214] Surveillance is started at 10–15 years of age. For adult patients aged ≥18 years, initial surveillance is performed with blood pressure measurement, medical interview for PPGL-related symptoms, biochemical tests (plasma free metanephrine and normetanephrine are preferred to urine biochemistry), MRI (head-and-neck and abdominal-to-pelvic MRI), and PET-CT. In subsequent surveillances, blood pressure

	measurement, medical interview for related symptoms, and biochemical tests (plasma free metanephrine fraction is preferred to urinary fraction) are performed annually, and MRI (head-and-neck and chest-to-pelvic MRI) is performed every 2–3 years. The methods and intervals of surveillance differ for pediatric patients, for which the guidelines above should be referred to. No additional imaging tests are recommended for renal cell carcinoma or GIST, and patients should be examined simultaneously with imaging tests for PPGL.
Supplementary information	Cancer types whose penetration rate is unknown although their correlation with onset risk has been pointed out: GIST and renal cell carcinoma *SDHC*-related hereditary pheochromocytoma and paraganglioma often develop with head and neck paragangliomas (65.2%), but thoracoabdominal paragangliomas (28.2%) and pheochromocytomas (6.5%) may also develop[223]. Among *SDHC* GPV carriers, the detection rate of related tumors during follow-up was reported to be 3.2% (1/31 cases)[222] and 3.6% (1/28 cases)[221].

1

1 *SDHD*

2

Disease	PHEOCHROMOCYTOMA/PARAGANGLIOMA SYNDROME 1; PPGL1 (OMIM 168000) (GRJ hereditary paraganglioma and pheochromocytoma syndrome)
Inheritance pattern	Autosomal dominant inheritance (paternal inheritance; see 'Supplementary information')
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	Pheochromocytoma and paraganglioma: 43.2% at 60 years of age[219] (see 'Supplementary information')
Domestic clinical practice guidelines	Clinical Practice Guidelines for Pheochromocytoma and Paraganglioma, 2018 Edition. The Japan Endocrine Society[125]
Clinical management recommended by domestic clinical practice guidelines	For cancer-free GPV carriers, surveillance is started 10 years earlier than the onset age of the affected family member with the earliest onset, with the following: medical examination, annual measurement of blood free (or urinary) metanephrine, annual CT or MRI, and triennial ^{123}I-MIBG scintigraphy (Note: This is only tentative, as it is not based on prospective studies.)
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	1. NCCN Guidelines®, Neuroendocrine and Adrenal Tumors. Version 1. 2024-Jun 20, 2024[126] Surveillance for pheochromocytoma and paraganglioma is started at 10–15 years of age. Blood pressure is measured at every medical examination. Plasma free or 24-hour urinary metanephrine fraction is measured annually. Whole-body MRI is performed every 2–3 years. Abdominal MRI, MRI of the skull base to the neck, and chest CT are performed if whole-body MRI is not available (to be considered). 2. International consensus on initial screening and follow-up of asymptomatic SDHx mutation carriers (2021)[214] For patients inheriting *SDHD* GPV from the paternal side, surveillance is started at 10–15 years of age (there is no consensus on surveillance for patients inheriting *SDHD* GPV from the maternal side). For adult patients aged ≥18 years, initial surveillance is performed with blood pressure measurement, medical interview for PPGL-related symptoms, biochemical tests (plasma free metanephrine and normetanephrine are preferred to urine biochemistry), MRI (head-and-neck and abdominal-to-pelvic MRI), and PET-CT. In subsequent surveillances, blood pressure measurement, medical interview for related symptoms, and biochemical

	tests (plasma free metanephrine fraction is preferred to urinary fraction) are performed annually, and MRI (head-and-neck and chest-to-pelvic MRI) is performed every 2–3 years. The methods and intervals of surveillance differ for pediatric patients, for which the guidelines above should be referred to. No additional imaging tests are recommended for renal cell carcinoma or GIST, and patients should be examined simultaneously with imaging tests for PPGL. 3. Clinical consensus guideline on the management of phaeochromocytoma and paraganglioma in patients harbouring germline SDHD pathogenic variants (2023)[224] This is a consensus guideline for the treatment of pheochromocytoma and paraganglioma in *SDHD* GPV carriers (cancer-affected patients). Biochemical tests include measurements of plasma or urine metanephrine and plasma methoxytyramine (not approved in Japan). Imaging tests include head-and-neck MRI for the surveillance of multifocality and tumor progression, as well as PET-CT for total-body examination (somatostatin receptor scintigraphy, if possible). Watchful waiting that considers the risk of complications from surgery is selected, depending on the case.
Supplementary information	Cancer types whose penetration rate is unknown although their correlation with onset risk has been pointed out: GIST, renal cell carcinoma, and pituitary adenoma Even if it is inherited from the maternal side, there is a lifetime risk of developing PPGL (<5%)[214, 225]. *SDHD*-related hereditary pheochromocytoma and paraganglioma often develop with head and neck paragangliomas (they occur synchronously, metachronously, and multifocally)[238]. Surveillance studies of individuals carrying GPV in *SDHx (SDHB*, *SDHD*, and *SDHC)* reported high detection rates of pheochromocytoma and paraganglioma during follow-up among *SDHD* GPV carriers, at 40% (14/35 cases)[221] and 57% (27/47 cases)[222].

1

SMAD4

Disease	JUVENILE POLYPOSIS SYNDROME; JPS (OIM 174900) (GRJ juvenile polyposis syndrome)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.01%[1)]
Risk of cancer onset (penetration rate)	The overall risk of cancer onset in patients with juvenile polyposis syndrome (JPS) is 86.2% (gastric cancer: 73.0%, colorectal cancer: 51.1%, small intestinal cancer: rare, pancreatic cancer: rare)[50)].
Domestic clinical practice guidelines	Clinical Practice Guidelines for Juvenile Polyposis Syndrome in Children and Adults (2020 Edition)[51)]
Clinical management recommended by domestic clinical practice guidelines	**Gastrointestinal (malignant) tumor**: For suspected cases, upper gastrointestinal endoscopy and colonoscopy are performed 12–15 years of age. Responses taken after definitive diagnosis vary depending on the number of polyps and the phenotype, such as gastric- and colorectal-localized types, and upper gastrointestinal endoscopy and colonoscopy are performed every 1–3 years. Surveillance is started early if the patient exhibits symptoms caused by polyps. If small-intestinal bleeding or protein-losing gastroenteropathy is suspected, balloon small-intestinal endoscopy, capsule endoscopy, or CT enterography is performed. Polyps with a size of ≥5 mm are treated with endoscopic resection, and partial resection of the intestinal tract is considered for patients with multiple polyps that cannot be managed with endoscopic therapy. Prophylactic gastrectomy is considered for patients carrying *SMAD4* GPV with the gastric-localized phenotype, who present with iron-deficiency anemia or hypoalbuminemia that are refractory to medical treatment, because of the high incidence of gastric cancer and the difficulty of preoperative cancer diagnosis.
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are	ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes (2015)[52)] There are no additional recommended items.

listed.	
Supplementary information	According to the ACG and NCCN guidelines, the risk of developing gastric cancer among patients with juvenile polyposis syndrome is 21%[32, 52, 62]. *SMAD4* GPV carriers have a high rate of developing gastric lesions, and it has been reported that 30% of patients with the gastric-localized phenotype develop gastric cancer. Skin and nasal mucosal vascular lesions, pulmonary arteriovenous malformations, cardiac macrovascular lesions, intracranial vascular lesions, and hepatic vascular lesions due to hereditary hemorrhagic telangiectasia (HHT) have been reported to occur in 71–81% of patients (JPS/HHT syndrome, OMIM 175050)[226, 227]. Annual cardiovascular surveillance has been proposed, but the frequency and testing methods of surveillance remain to be determined[52]. Reference #50 is a domestic case report review of JPS.

1

STK11

Disease	PEUTZ-JEGHERS SYNDROME; PJS (OMIM 175200) (GRJ Peutz-Jeghers syndrome)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	0.01% (Japan)[1)]
Risk of cancer onset (penetration rate)	[Individuals aged ≤70 years] gastric cancer: 24.0%[228)], duodenal carcinoma: 10.3%[228)], jejunal and ileal carcinoma: 13.8%[228)], colorectal cancer: 36.4%[228)], breast cancer: 19.3%[228)], uterine cancer: 46.5%[228)], ovarian cancer: 10.1%[228)], pancreatic cancer: 29.4%[228)], gallbladder cancer: 10.5%[228)], lung cancer: 7.6%[228)], thyroid cancer: 2.7%[228)]. [Individuals aged 15–64 years] testicular tumor: 9%[229)].
Domestic clinical practice guidelines	Clinical Practice Guidelines for Peutz-Jeghers Syndrome in Children and Adults (2020 Edition)[230)]
Clinical management recommended by domestic clinical practice guidelines	**Gastrointestinal tumor**: Endoscopy of the entire gastrointestinal tract, including the small intestine, is performed around the age of 8 years, even if the patient is asymptomatic. If the patient has polyps, endoscopy and other examinations are performed every 1–3 years. If symptoms caused by gastrointestinal polyps are present, endoscopy is performed, even for those aged <8 years. Small-intestinal polyps with a size of ≥10–15 mm, which cause small-intestinal intussusception, are treated with endoscopic resection from childhood. Polyps with a size of ≥10 mm in the stomach and large intestine are treated with endoscopic resection. For patients aged ≥50 years, upper gastrointestinal endoscopy and colonoscopy are performed every 1–2 years. **Breast cancer**: Self-examination is performed starting around the age of 18 years, and breast MRI/ultrasonography is performed starting at 25 years of age. Mammography is performed annually after 50 years of age. **Pancreatic cancer**: MRCP or EUS is performed every 1–2 years starting at 30 years of age. **Cervical adenocarcinoma and uterine body cancer**: Cervical smear and internal examination/ultrasonography are performed every 1–3 years starting at 18–25 years of age. **Ovarian tumor**: Internal examination/ultrasonography is performed annually starting at 18–25 years of age. **Lung cancer**: Smoking cessation is recommended, and it is started earlier than general medical examination (to be considered). **Testicular tumor**: Palpation is performed from infancy. Ultrasonography is performed for patients with abnormal palpation findings or gynecomastia.

Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	NCCN Guidelines®, Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version 1. 2024-August 8, 2024[32] **Ovary**: Patients are examined for the presence or absence of precocious puberty (<8 years of age). **Uterine body**: Internal examination is performed annually starting at 18–20 years of age. Endometrial histological diagnosis is performed for patients with abnormal bleeding. **Lungs**: Education on symptoms and smoking cessation is provided. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes (2015)[52] There are no additional recommended items. **Uterine body cancer**: Internal examination and transvaginal (transabdominal) ultrasonography are performed annually starting at 25 years of age.
Supplementary information	It was reported that 29% of patients with Peutz-Jeghers syndrome were isolated cases with no family history[231]. **Cervical adenocarcinoma and uterine body cancer**: HPV-independent gastric adenocarcinomas and minimally deviated adenocarcinomas are characteristic of the syndrome. **Ovarian tumor**: Ovarian sex-cord tumors with annular tubules and ovarian mucinous tumors are characteristic of the syndrome. **Testicular tumor**: Large-cell calcifying Sertoli cell tumors are characteristic of the syndrome.

1

TMEM127

Disease	PHEOCHROMOCYTOMA, SUSCEPTIBILITY TO (OMIM 171300) (GRJ hereditary paraganglioma and pheochromocytoma syndrome)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	Pheochromocytoma and paraganglioma: unknown (see 'Supplementary information)
Domestic clinical practice guidelines	Clinical Practice Guidelines for Pheochromocytoma and Paraganglioma, 2018 Edition. The Japan Endocrine Society[125]
Clinical management recommended by domestic clinical practice guidelines	Surveillance is started 10 years earlier than the onset age of the affected family member with the earliest onset, with the following: medical examination, annual measurement of blood free (or urinary) metanephrine, annual CT or MRI, and triennial ^{123}I-MIBG scintigraphy (Note: This is only tentative, as it is not based on prospective studies.)
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	1. NCCN Guidelines®, Neuroendocrine and Adrenal Tumors. Version 1. 2024-Jun 20, 2024[126] Surveillance for pheochromocytoma and paraganglioma is started at 10–15 years of age. Blood pressure is measured at every medical examination. Plasma free or 24-hour urinary metanephrine fraction is measured annually. Whole-body MRI is performed every 2–3 years. Abdominal MRI, MRI of the skull base to the neck, and chest CT are performed if whole-body MRI is not available (to be considered). 2. Personalized Management of Pheochromocytoma and Paraganglioma (2022)[127] If the patient has a history of pheochromocytoma, clinical evaluation and biochemical tests are performed annually, and abdominal-to-pelvic MRI is performed every 5 years.
Supplementary information	Cancer types whose penetration rate is unknown although their correlation with onset risk has been pointed out: renal cell carcinoma In the observation of 6 family generations with a *TMEM127* variant (c.410-2A>C), the penetration rate of pheochromocytoma was reported to be 0% at 0–20 years of age, 3% at 21–30 years of age, 15% at 31–40 years of age, 24% at 41–50 years of age, and 32% at 51–65 years of age[232]. In the majority (85.5%) of cases, *TMEM127*-related hereditary pheochromocytoma and paraganglioma syndrome develops with pheochromocytoma, but the development of head and neck/retroperitoneal paragangliomas has also been

	reported[233].

1

TP53

Disease	LI-FRAUMENI SYNDROME; LFS (OMIM 151623) (GRJ Li-Fraumeni syndrome)
Inheritance pattern	Autosomal dominant inheritance
GPV Frequency	0.03%[1], 1/500–20,000 persons (overseas)[234-237]
Risk of cancer onset (penetration rate)	All cancer types: approximately 75% in men and nearly 100% in women[238, 239]. Breast cancer: 25.0–59.6%[238, 239], brain tumor: 5.4–13.0%[238, 239], soft tissue sarcoma: 14.3–26.7%[238, 239], osteosarcoma: 6.3–15.5%[238, 239], adrenocortical cancer: 1.7–13.0%[238, 239].
Domestic clinical practice guidelines	Clinical Practice Guidelines for Li-Fraumeni Syndrome, 2019 Edition. Group for "Research for the Implementation of Genomic Medicine System for Hereditary Tumors Occurring in Childhood"[240]
Clinical management recommended by domestic clinical practice guidelines	**Systemic evaluation**: Systemic evaluation is performed every 3–4 months in children (birth to 18 years of age) and every 6 months in adults. **Adrenocortical cancer**: Abdominal and pelvic ultrasonography is performed every 3–4 months from birth to 18 years of age. **Brain tumor**: MRI (contrast-enhanced MRI for initial examination) is performed annually from birth. **Bone and soft tissue tumors**: Whole-body MRI is performed annually from birth, and abdominal and pelvic ultrasonography is performed every 3–4 months (every 12 months after adulthood, alternating with whole-body MRI). **Breast cancer**: Breast examination is performed every 6 months starting at 20 years of age, and breast MRI is performed annually (alternating with whole-body MRI) between the ages of 20 and 75 years. **Digestive system cancer**: Upper and lower gastrointestinal endoscopy is performed every 2–5 years starting at 25 years of age. **Malignant melanoma**: Dermatological examination is performed annually starting at 18 years of age.
Clinical management recommended by international clinical practice guidelines Only items not described	1. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes (2020)[241] 2. UKCGG Consensus Group guidelines for the management of patients with constitutional TP53 pathogenic variants (2020)[242] Routine colonoscopy is considered if the patient has a family history of colorectal cancer or polyposis. 3. NCCN Guidelines®,Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 3. 2024-February 12, 2024[38] 4. SEOM clinical guideline on heritable TP53-related cancer syndrome [2022] (2023)[243]

in domestic practice guidelines are listed.	Blood count examination is performed annually if the patient has a history of taking drugs that pose the risk of developing leukemia.
Supplementary information	—

1

TSC1

Disease	TUBEROUS SCLEROSIS 1; TSC1 (OMIM 191100) (GRJ tuberous sclerosis)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown (see 'Supplementary information')
Risk of cancer onset (penetration rate)	Cardiac rhabdomyoma: 50% (from fetal to infant stage)[244], facial angiofibroma: 80% (≤5 years)[244], central nervous system lesion (subependymal giant cell astrocytoma): 5–15%[244], renal lesion (angiomyolipoma): 60–80%[244], pulmonary lesion (lymphangioleiomyomatosis): 80% in women (<40 years of age) and 10–12% in men[244]
Domestic clinical practice guidelines	1. Diagnostic Criteria and Treatment Guidelines for Tuberous Sclerosis (Revised Edition). Committee for the Revision of "Diagnostic Criteria and Treatment Guidelines for Tuberous Sclerosis" (ed.)[244] 2. Clinical Practice Guidelines for Brain Tumor: Pediatric Brain Tumor, 2021 Edition. Japan Society for Neuro-Oncology (ed.)[164] 3. Clinical Practice Guidelines for Renal Angiomyolipoma Associated with Tuberous Sclerosis, 2016 Edition. Japanese Urological Association and Japanese Society of Tuberous Sclerosis Complex (ed.)[245]
Clinical management recommended by domestic clinical practice guidelines	**Cardiac rhabdomyoma**: Cardiac rhabdomyomas appear during the fetal stage and reach the largest size at birth. If they are detected by prenatal ultrasonography (especially multiple rhabdomyomas), fetal cardiac ultrasonography is performed periodically because of the high risk of TSC and postnatal cardiac manifestations. For pediatric patients aged <3 years, cardiac ultrasonography and electrocardiography (12-lead electrocardiography is particularly recommended) are performed. For asymptomatic pediatric patients, cardiac ultrasonography is performed annually. **Renal lesion (angiomyolipoma)**: Ultrasonography is performed annually if the patient has developed renal lesions. **Central nervous system lesion (subependymal giant cell astrocytoma)**: It is desirable that brain MRI examination be performed every 1–3 years until 25 years of age.
Clinical management recommended by international clinical practice guidelines Only items not	1. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations (2021)[246] There are no additional recommended items. 2. NCCN Guidelines® Kidney Cancer. Version 3. 2024-Mar 11, 2024[47] **Renal lesion**: Abdominal MRI (preferred) or CT, with and without IV contrast, is performed every 1–3 years starting at 12 years of age.

described in domestic practice guidelines are listed.	
Supplementary information	The frequency of TSC patients was estimated to be 1/6,760–13,520 births[247, 248]. A quarter of *TSC1/2* GPV carriers have TSC1[249]. Two-thirds (137/200) of affected patients have de novo mutations[249].

1

TSC2

Disease	TUBEROUS SCLEROSIS 2; TSC2 (OMIM 613254) (GRJ tuberous sclerosis)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown (see 'Supplementary information')
Risk of cancer onset (penetration rate)	Cardiac rhabdomyoma: 50% (from fetal to infant stage)[244], facial angiofibroma: 80% (≤5 years)[244], central nervous system lesion (subependymal giant cell astrocytoma): 5–15%[244], renal lesion (angiomyolipoma): 60–80%[244], pulmonary lesion (lymphangioleiomyomatosis): 80% in women (<40 years of age) and 10–12% in men[244]
Domestic clinical practice guidelines	1. Diagnostic Criteria and Treatment Guidelines for Tuberous Sclerosis (Revised Edition). Committee for the Revision of "Diagnostic Criteria and Treatment Guidelines for Tuberous Sclerosis" (ed.)[244] 2. Clinical Practice Guidelines for Brain Tumor: Pediatric Brain Tumor, 2021 Edition. Japan Society for Neuro-Oncology (ed.)[164] 3. Clinical Practice Guidelines for Renal Angiomyolipoma Associated with Tuberous Sclerosis, 2016 Edition. Japanese Urological Association and Japanese Society of Tuberous Sclerosis Complex (ed.)[245]
Clinical management recommended by domestic clinical practice guidelines	**Cardiac rhabdomyoma**: Cardiac rhabdomyomas typically appear during the fetal stage and reach their largest size at birth. If detected by prenatal ultrasonography, especially when multiple rhabdomyomas are present, fetal cardiac ultrasonography should be performed periodically because of the high risk of TSC and postnatal cardiac manifestations. For pediatric patients younger than 3 years, cardiac ultrasonography and electrocardiography, particularly 12-lead electrocardiography, should be performed. For asymptomatic pediatric patients, cardiac ultrasonography should be performed annually. **Renal lesion (angiomyolipoma)**: If renal lesions are present, ultrasonography should be performed annually. **Central nervous system lesion (subependymal giant cell astrocytoma)**: Brain MRI should be performed every 1–3 years until 25 years of age.
Clinical management recommended by international clinical practice guidelines Only items not	1. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations (2021)[246] There are no additional recommended items. 2. NCCN Guidelines® Kidney Cancer. Version 3. 2024-Mar 11, 2024[47] **Renal lesion**: Abdominal MRI (preferred) or CT, with and without IV contrast, is performed every 1–3 years starting at 12 years of age.

described in domestic practice guidelines are listed.	
Supplementary information	The frequency of TSC patients was estimated to be 1/6,760–13,520 births[247, 248]. Three-quarters of *TSC1/2* GPV carriers have TSC2[249]. Two-thirds (137/200) of affected patients have de novo mutations[249]. Some TSC patients present with features of both TSC caused by the deletion of *TSC2* and autosomal dominant polycystic kidney disease (ADPKD) caused by the deletion of *PKD1* (TSC2/PKD1 contiguous gene syndrome).

1

1 *VHL*

2

Disease	VON HIPPEL-LINDAU SYNDROME; VHLS (OMIM 193300) (GRJ von Hippel-Lindau disease)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	1/36,000 births (East Anglia, United Kingdom)[250]
Risk of cancer onset (penetration rate)	Central nervous system hemangioblastoma: 44–72% (cerebellum)[250], 10–25% (brain stem)[250], 13–50% (spinal cord)[250]. Endolymphatic sac tumor: 10%[250]. Retinal hemangioblastoma: 25–60%[250]. Pancreatic tumor/cyst: 35–70%[250]. Renal cell carcinoma/cyst: 25–60%. Pheochromocytoma and paraganglioma: 10–20%[250]. Epididymal cystadenoma: 25–60%[250].
Domestic clinical practice guidelines	1. Clinical Practice Guidelines for von Hippel-Lindau Disease, 2017 Edition. Group for "Research on the Actual Status and Standardization of Medical Treatment of Hereditary Diseases Causing Various Endocrine Abnormalities (Multiple Endocrine Neoplasia and von Hippel-Lindau Disease)"[251] 2. Clinical Practice Guide for von Hippel-Lindau Disease (2024 Edition) Group for "Comprehensive Research on von Hippel-Lindau Disease for the Investigation of the Actual Condition, Establishment of Medical Treatment System, and Improvement of QOL"[252]
Clinical management recommended by domestic clinical practice guidelines	**Central nervous system hemangioblastoma**: Cerebrospinal MRI is performed every 1–2 years starting at 11 years of age. **Retinal hemangioblastoma**: Fundus examination is performed annually starting from birth. **Pancreatic neuroendocrine tumor**: Abdominal contrast-enhanced CT (dynamic CT) is performed every 2–3 years starting at 15 years of age. **Renal cell carcinoma**: Ultrasonography/MRI is performed annually starting at 15 years of age. **Pheochromocytoma and paraganglioma**: Medical interview, blood pressure measurement, and heart rate measurement should be performed annually, starting at 2 years of age. Biochemical tests, including blood free metanephrine fraction and 24-hour urinary metanephrine, should be performed annually, starting at 5 years of age. Abdominal contrast-enhanced MRI should be performed every 2 years, starting at 15 years of age. **Epididymal cystadenoma**: Palpation of the scrotum is performed every 2–3 years starting in the teenage years.
Clinical management recommended by	Guidelines for surveillance of patients with von Hippel-Lindau disease: Consensus statement of the International VHL Surveillance Guidelines Consortium and VHL Alliance (2023)[253] Fundus examination is performed every 6–12 months starting <1 year of age.

international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	Cerebrospinal MRI and hearing tests should be performed every 2 years, beginning at 11 years of age. Abdominal MRI should be performed every 2 years, starting at 15 years of age, and MRI of the inner auditory canal should be performed at age 15. If no findings characteristic of VHL are observed by age 65, surveillance, other than physical and fundus examinations, may be discontinued.
Supplementary information	A study of 206 Japanese families showed that 20% had large deletions detected by MLPA and that mosaic mutations were detected in 3 cases[254].

1

WT1

Disease	WILMS TUMOR 1; WT1 (OMIM 194070) (GRJ Wilms tumor predisposition)
Inheritance pattern	Autosomal dominant inheritance
GPV frequency	Unknown
Risk of cancer onset (penetration rate)	Wilms tumor: 35.8–37.7%[255, 256] (truncating variants > missense variants ≫ intron 9 variants)[257], gonadoblastoma: 1.9–4.9%[255, 256]
Domestic clinical practice guidelines	None
Clinical management recommended by domestic clinical practice guidelines	None
Clinical management recommended by international clinical practice guidelines Only items not described in domestic practice guidelines are listed.	Wilms tumor surveillance in at-risk children: Literature review and recommendations from the SIOP-Europe Host Genome Working Group and SIOP Renal Tumor Study Group (2021)[257] For high-risk variant carriers, abdominal ultrasonography is performed from the time of diagnosis (or 3 months of age) until 7 years of age.
Supplementary information	The GPV frequency is unknown, but approximately 500 cases have been reported[258]. **Non-tumor clinical findings**: ・Glomerulopathy ・Disorder of testicular development ・Congenital anomalies of the kidney and urinary tract (CAKUT)

■ References

1) Usui Y, Taniyama Y, Endo M, et al. Helicobacter pylori, Homologous-Recombination Genes, and Gastric Cancer. N Engl J Med. 2023;388(13):1181-90. [PMID: 36988593]
2) Fujita M, Liu X, Iwasaki Y, et al. Population-based Screening for Hereditary Colorectal Cancer Variants in Japan. Clin Gastroenterol Hepatol. 2020;20(9):2132-41. e9. [PMID: 33309985]
3) Bussey HJR. Familial polyposis coli: family studies, histopathology, differential diagnosis, and results of treatment. Johns Hopkins University Press, Baltimore, 1975.
4) Yamaguchi T, Ishida H, Ueno H, et al. Upper gastrointestinal tumours in Japanese familial adenomatous polyposis patients. Jpn J Clin Oncol. 2016;46(4):310-5. [PMID: 26819281]
5) Jagelman DG, DeCosse JJ, Bussey HJ. Upper gastrointestinal cancer in familial adenomatous polyposis. Lancet. 1988;1(8595):1149-51. [PMID: 2896968]
6) Iwama T, Mishima Y, Utsunomiya J. The impact of familial adenomatous polyposis on the tumorigenesis and mortality at the several organs. Its rational treatment. Ann Surg. 1993;217(2):101-8. [PMID: 8382467]
7) Park SY, Ryu JK, Park JH, et al. Prevalence of gastric and duodenal polyps and risk factors for duodenal neoplasm in korean patients with familial adenomatous polyposis. Gut Liver. 2011;5(1):46-51. [PMID: 21461071]
8) Maehata Y, Esaki M, Hirahashi M, et al. Duodenal adenomatosis in Japanese patients with familial adenomatous polyposis. Dig Endosc. 2014;26(Suppl 2):30-4. [PMID: 24750145]
9) Saito Y, Hinoi T, Ueno H, et al. Risk Factors for the Development of Desmoid Tumor After Colectomy in Patients with Familial Adenomatous Polyposis: Multicenter Retrospective Cohort Study in Japan. Ann Surg Oncol. 2016;23(Suppl 4):559-65. [PMID: 27387679]
10) Church J, Xhaja X, LaGuardia L, et al. Desmoids and genotype in familial adenomatous polyposis. Dis Colon Rectum. 2015;58(4):444-8. [PMID: 25751801]
11) Hartley JE, Church JM, Gupta S, et al. Significance of incidental desmoids identified during surgery for familial adenomatous polyposis. Dis Colon Rectum. 004;47(3):334-8;discussion 339-40. [PMID: 14991495]
12) Schiessling S, Kihm M, Ganschow P, et al. Desmoid tumour biology in patients with familial adenomatous polyposis coli. Br J Surg. 2013;100(5):694-703. [PMID: 23334997]
13) Friedl W, Aretz S. Familial adenomatous polyposis: experience from a study of 1164 unrelated german polyposis patients. Hered Cancer Clin Pract. 2005;3(3):95-114. [PMID: 20223039]
14) Nieuwenhuis MH, Lefevre JH, Bülow S, et al. Family history, surgery, and APC mutation are risk factors for desmoid tumors in familial adenomatous polyposis: an international cohort study. Dis Colon Rectum. 2011;54(10):1229-34. [PMID: 21904137]

15) Walter T, Zhenzhen Wang C, Guillaud O, et al. Management of desmoid tumours: A large national database of familial adenomatous patients shows a link to colectomy modalities and low efficacy of medical treatments. United European Gastroenterol J. 2017;5(5):735-41 [PMID: 28815038]
16) Feng X, Milas M, O'Malley M, et al. Characteristics of benign and malignant thyroid disease in familial adenomatous polyposis patients and recommendations for disease surveillance. Thyroid. 2015;25(3):325-32. [PMID: 25585202]
17) Jarrar AM, Milas M, Mitchell J, et al. Screening for thyroid cancer in patients with familial adenomatous polyposis. Ann Surg. 2011;253(3):515-21. [PMID: 21173694]
18) Sada H, Hinoi T, Ueno H, et al. Prevalence of and risk factors for thyroid carcinoma in patients with familial adenomatous polyposis: results of a multicenter study in Japan and a systematic review. Surg Today. 2019;49(1):72-81. [PMID: 30182306]
19) Truta B, Allen BA, Conrad PG, et al. Genotype and phenotype of patients with both familial adenomatous polyposis and thyroid carcinoma. Fam Cancer. 2003;2(2):95-9 [PMID: 14574158]
20) Chenbhanich J, Atsawarungruangkit A, Korpaisarn S, et al. Prevalence of thyroid diseases in familial adenomatous polyposis: a systematic review and meta-analysis. Fam Cancer. 2019;18 (1):53-62. [PMID: 29663106]
21) Shiroky JS, Lerner-Ellis JP, Govindarajan A, et al. Characteristics of Adrenal Masses in Familial Adenomatous Polyposis. Dis Colon Rectum. 2018;61(6):679-85. [PMID: 29377868]
22) Smith TG, Clark SK, Katz DE, et al. Adrenal masses are associated with familial adenomatous Dis Colon Rectum. 2000;43(12):1739-42. [PMID: 11156460]
23) Marchesa P, Fazio VW, Church JM, et al. Adrenal masses in patients with familial adenomatous polyposis. Dis Colon Rectum. 1997;40(9):1023-8. [PMID: 9293929]
24) Attard TM, Giglio P, Koppula S, et al. Brain tumors in individuals with familial adenomatous polyposis: a cancer registry experience and pooled case report analysis. Cancer. 2007;109(4):761-6. [PMID: 17238184]
25) de Oliveira JC, Viana DV, Zanardo C, et al. Genotype-phenotype correlation in 99 familial adenomatous polyposis patients: A prospective prevention protocol. Cancer Med. 2019;8(5):2114-22. [PMID: 30897307]
26) Trobaugh-Lotrario AD, López-Terrada D, Li P, et al. Hepatoblastoma in patients with molecularly proven familial adenomatous polyposis: Clinical characteristics and rationale for surveillance screening. Pediatr Blood Cancer. 2018;65(8):e27103. [PMID: 29719120]
27) Aretz S, Koch A, Uhlhaas S, et al. Should children at risk for familial adenomatous polyposis be screened for hepatoblastoma and children with apparently sporadic hepatoblastoma be screened for APC germline mutations? Pediatr Blood Cancer. 2006;47(6):811-8. [PMID: 16317745]

28) Kennedy RD, Potter DD, Moir CR, et al. The natural history of familial adenomatous polyposis syndrome: a 24 year review of a single center experience in screening, diagnosis, and outcomes. J Pediatr Surg. 2014;49(1):82-6. [PMID: 24439586]
29) Giardiello FM, Offerhaus GJ, Krush AJ, et al. Risk of hepatoblastoma in familial adenomatous polyposis. J Pediatr. 1991;119(5):766-8. [PMID: 1658283]
30) Hughes LJ, Michels VV. Risk of hepatoblastoma in familial adenomatous polyposis. Am J Med Genet. 1992;43(6):1023-5. [PMID: 1329510]
31) Japanese Society for Cancer of the Colon and Rectum (ed.). Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition. Kanehara Publishing Co., Ltd.
32) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Version1, 2024.
33) Murata M, Utsunomiya J, Iwama T, et al. Frequency of adenomatosis coli in Japan. Jinrui Idengaku Zasshi. 1981;26(1):19-30. [PMID: 7265541]
34) Repak R, Kohoutova D, Podhola M, et al. The first European family with gastric adenocarcinoma and proximal polyposis of the stomach: case report and review of the literature. Gastrointest Endosc. 2016;84(4):718-25. [PMID: 27343414]
35) Kasugai Y, Kohmoto T, Taniyama Y, et al. Association between germline pathogenic variants and breast cancer risk in Japanese women: The HERPACC study. Cancer Sci. 2022;113(4): 1451-62. [PMID: 35218119]
36) Dorling L, Carvalho S, Allen J, et al.; Breast Cancer Association Consortium. Breast Cancer Risk Genes-Association Analysis in More than 113,000 Women. N Engl J Med. 2021;384(5): 428-39. [PMID: 33471991]
37) Mavaddat N, Dorling L, Carvalho S, et al.; Breast Cancer Association Consortium. Pathology of Tumors Associated With Pathogenic Germline Variants in 9 Breast Cancer Susceptibility Genes. JAMA Oncol. 2022;8(3):e216744. [PMID: 35084436]
38) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic. Version 3. 2024.
39) Bernstein JL, Teraoka S, Southey MC, et al. Population-based estimates of breast cancer risks associated with ATM gene variants c.7271T＞G and c.1066-6T＞G(IVS10-6T＞G) from the Breast Cancer Family Registry. Hum Mutat. 2006;27(11):1122-8. [PMID: 16958054]
40) Hsu FC, Roberts NJ, Childs E, et al. Risk of Pancreatic Cancer Among Individuals With Pathogenic Variants in the ATM Gene. JAMA Oncol. 2021;7(11):1664-8. [PMID: 34529012]
41) Marvin ML, Mazzoni SM, Herron CM, et al. AXIN2-associated autosomal dominant ectodermal dysplasia and neoplastic syndrome. Am J Med Genet A. 2011;155A(4):898-902. [PMID: 21416598]

42) Macklin-Mantia SK, Hines SL, Chaichana KL, et al. Case report expanding the germline AXIN2-related phenotype to include olfactory neuroblastoma and gastric adenoma. BMC Med Genet. 2020;21(1):161. [PMID: 32807118]
43) Pilarski R, Carlo MI, Cebulla C, et al. BAP1 Tumor Predisposition Syndrome. Adam MP, Feldman J, Mirzaa GM, et al (eds). GeneReviews® [Internet], Seattle (WA): University of Washington Oct 13, 2016 [Last revision: March 24, 2022]
https://www.ncbi.nlm.nih.gov/books/NBK390611/(accessed 2024-08-26)
44) Haugh AM, Njauw CN, Bubley JA, et al. Genotypic and Phenotypic Features of BAP1 Cancer Syndrome: A Report of 8 New Families and Review of Cases in the Literature. JAMA Dermatol. 2017;153(10):999-1006. [PMID: 28793149]
45) Walpole S, Pritchard AL, Cebulla CM, et al. Comprehensive Study of the Clinical Phenotype of Germline BAP1 Variant-Carrying Families Worldwide. J Natl Cancer Inst. 2018;110(12): 1328-41. [PMID: 30517737]
46) Rai K, Pilarski R, Cebulla CM, et al. Comprehensive review of BAP1 tumor predisposition syndrome with report of two new cases. Clin Genet. 2016;89(3):285-94. [PMID: 26096145]
47) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Kidney Cancer Version 3. 2024.
48) Star P, Goodwin A, Kapoor R, et al. Germline BAP1-positive patients: the dilemmas of cancer surveillance and a proposed interdisciplinary consensus monitoring strategy. Eur J Cancer. 2018;92:48-53. [PMID: 29413689]
49) Hu C, Hart SN, Gnanaolivu R, et al. A Population-Based Study of Genes Previously Implicated in Breast Cancer. N Engl J Med. 2021;384(5):440-51. [PMID: 33471974]
50) Ishida H, Ishibashi K, Iwama T. Malignant tumors associated with juvenile polyposis syndrome in Japan. Surg Today. 2018;48(3):253-63. [PMID: 28550623]
51) Matsumoto T, Arai M, Iwama T, et al. Clinical Practice Guidelines for Juvenile Polyposis Syndrome in Children and Adults (2020 Edition). Journal of Hereditary Tumors. 2020;20(2):79-92.
52) Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223-62; quiz 263. [PMID: 25645574]
53) Singh AD, Gupta A, Mehta N, et al. Occurrence of gastric cancer in patients with juvenile polyposis syndrome: a systematic review and meta-analysis. Gastrointest Endosc. 2023;97(3):407-14. e1. [PMID: 36265529]
54) Blatter R, Tschupp B, Aretz S, et al. Disease expression in juvenile polyposis syndrome: a retrospective survey on a cohort of 221 European patients and comparison with a literature-derived cohort of 473 SMAD4/BMPR1A pathogenic variant carriers. Genet Med. 2020;22(9):1524-32. [PMID: 32398773]

55) Dahdaleh FS, Carr JC, Calva D, et al. Juvenile polyposis and other intestinal polyposis syndromes with microdeletions of chromosome 10q22-23. Clin Genet. 2012;81(2):110-6 [PMID: 21834858]
56) Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007;25 (11):1329-33. [PMID: 17416853]
57) Ford D, Easton DF, Bishop DT, et al. Risks of cancer in BRCA1-mutation carriers. Breast Cancer Linkage Consortium. Lancet. 1994;343(8899):692-5. [PMID: 7907678]
58) King MC, Marks JH, Mandell JB, et al. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003;302(5645):643-6. [PMID: 14576434]
59) Mavaddat N, Peock S, Frost D, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst. 2013;105(11):812-22. [PMID: 23628597]
60) van den Broek AJ, van't Veer LJ, Hooning MJ, et al. Impact of Age at Primary Breast Cancer on Contralateral Breast Cancer Risk in BRCA1/2 Mutation Carriers. J Clin Oncol. 2016;34(5): 409-18. [PMID: 26700119]
61) Chen J, Bae E, Zhang L, et al. Penetrance of Breast and Ovarian Cancer in Women Who Carry a BRCA1/2 Mutation and Do Not Use Risk-Reducing Salpingo-Oophorectomy: An Updated Meta-Analysis. JNCI Cancer Spectr. 2020;4(4):pkaa029. [PMID: 32676552]
62) Li S, Silvestri V, Leslie G, et al. Cancer Risks Associated With BRCA1 and BRCA2 Pathogenic Variants. J Clin Oncol. 2022;40(14):1529-41. [PMID: 35077220]
63) Lecarpentier J, Silvestri V, Kuchenbaecker KB, et al. Prediction of Breast and Prostate Cancer Risks in Male BRCA1 and BRCA2 Mutation Carriers Using Polygenic Risk Scores. J Clin Oncol. 2017;35(20):2240-50. [PMID: 28448241]
64) Japan Organization of Hereditary Breast and Ovarian Cancer. Clinical Practice Guidelines for Hereditary Breast and Ovarian Cancer (HBOC), 2024 Edition. Kanehara Publishing Co., Ltd.
65) Tai YC, Domchek S, Parmigiani G, et al. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst. 2007;99(23):1811-4. [PMID: 18042939]
66) Nyberg T, Frost D, Barrowdale D, et al. Prostate Cancer Risks for Male BRCA1 and BRCA2 Mutation Carriers: A Prospective Cohort Study. Eur Urol. 2020;77(1):24-35 [PMID: 31495749]
67) Evans DG, Susnerwala I, Dawson J, et al. Risk of breast cancer in male BRCA2 carriers. J Med Genet. 2010;47(10):710-1. [PMID: 20587410]
68) Norquist BM, Harrell MI, Brady MF, et al. Inherited Mutations in Women With Ovarian Carcinoma. JAMA Oncol. 2016;2(4):482-90. [PMID: 26720728]
69) Weber-Lassalle N, Hauke J, Ramser J, et al. BRIP1 loss-of-function mutations confer high risk for familial ovarian cancer, but not familial breast cancer. Breast Cancer Res. 2018;20(1):7. [PMID: 29368626]

70) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Gastric Cancer Version 1. 2024.
71) Blair VR, McLeod M, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical practice guidelines. Lancet Oncol. 2020;21(8):e386-97. [PMID: 32758476]
72) Roberts ME, Ranola JMO, Marshall ML, et al. Comparison of CDH1 Penetrance Estimates in Clinically Ascertained Families vs Families Ascertained for Multiple Gastric Cancers. JAMA Oncol. 2019;5(9):1325-31. [PMID: 31246251]
73) Pharoah PD, Guilford P, Caldas C, et al.; International Gastric Cancer Linkage Consortium. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology. 2001;121(6):1348-53. [PMID: 11729114]
74) Truderung OA, Sagi JC, Semsei AF, et al. Melanoma susceptibility: an update on genetic and epigenetic findings. Int J Mol Epidemiol Genet. 2021;12(5):71-89. [PMID: 34853632]
75) Read J, Wadt KA, Hayward NK. Melanoma genetics. J Med Genet. 2016;53(1):1-14. [PMID: 26337759]
76) Soura E, Eliades PJ, Shannon K, et al. Hereditary melanoma: Update on syndromes and management: Genetics of familial atypical multiple mole melanoma syndrome. J Am Acad Dermatol. 2016;74(3):395-407;quiz 408-10. [PMID: 26892650]
77) Pauley K, Khan A, Kohlmann W, et al. Considerations for Germline Testing in Melanoma: Updates in Behavioral Change and Pancreatic Surveillance for Carriers of CDKN2A Pathogenic Variants. Front Oncol. 2022;12:837057. [PMID: 35372037]
78) Puntervoll HE, Yang XR, Vetti HH, et al. Melanoma prone families with CDK4 germline mutation: phenotypic profile and associations with MC1R variants. J Med Genet. 2013;50(4):264-70. [PMID: 23384855]
79) Begg CB, Orlow I, Hummer AJ, et al. Lifetime Risk of Melanoma in CDKN2A Mutation Carriers in a Population-Based Sample. J Natl Cancer Inst. 2005;97(20):1507-15. [PMID: 16234564]
80) Sargen MR, Helgadottir H, Yang XR, et al. Impact of Transcript (p16/p14ARF) Alteration on Cancer Risk in CDKN2A Germline Pathogenic Variant Carriers. JNCI Cancer Spectr. 2022;6(6):pkac074. [PMID: 36269225]
81) Vasen HF, Gruis NA, Frants RR, et al. Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16(p16-Leiden). Int J Cancer. 2000;87(6):809-11. [PMID: 10956390]
82) Klatte DCF, Boekestijn B, Wasser MNJM, et al. Pancreatic Cancer Surveillance in Carriers of a Germline CDKN2A Pathogenic Variant: Yield and Outcomes of a 20-Year Prospective Follow-Up. J Clin Oncol. 2022;40(28):3267-77. [PMID: 35658523]

83) Hu C, Hart SN, Polley EC, et al. Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer. JAMA. 2018;319(23):2401-9. [PMID: 29922827]
84) Chan SH, Chiang J, Ngeow J. CDKN2A germline alterations and the relevance of genotype-phenotype associations in cancer predisposition. Hered Cancer Clin Pract. 2021;19(1):21. [PMID: 33766116]
85) Momozawa Y, Iwasaki Y, Parsons MT, et al. Germline pathogenic variants of 11 breast cancer genes in 7,051 Japanese patients and 11,241 controls. Nat Commun. 2018;9(1):4083. [PMID: 30287823]
86) Momozawa Y, Iwasaki Y, Hirata M, et al. Germline Pathogenic Variants in 7636 Japanese Patients With Prostate Cancer and 12 366 Controls. J Natl Cancer Inst. 2020;112(4):369-76. [PMID: 31214711]
87) Hu C, Polley EC, Yadav S, et al. The Contribution of Germline Predisposition Gene Mutations to Clinical Subtypes of Invasive Breast Cancer From a Clinical Genetic Testing Cohort. J Natl Cancer Inst. 2020;112(12):1231-41. [PMID: 32091585]
88) Lowry KP, Geuzinge HA, Stout NK, et al. Breast Cancer Screening Strategies for Women With ATM, CHEK2, and PALB2 Pathogenic Variants: A Comparative Modeling Analysis. JAMA Oncol. 2022;8(4):587-96. [PMID: 35175286]
89) Cybulski C, Wokołorczyk D, Jakubowska A, et al. Risk of breast cancer in women with a CHEK2 mutation with and without a family history of breast cancer. J Clin Oncol. 2011;29(28):3747-52. [PMID: 21876083]
90) Fan X, Wynn J, Shang N, et al. Penetrance of Breast Cancer Susceptibility Genes From the eMERGE III Network. JNCI Cancer Spectr. 2021;5(4):pkab044. [PMID: 34377931]
91) Katona BW, Yurgelun MB, Garber JE, et al. A counseling framework for moderate-penetrance colorectal cancer susceptibility genes. Genet Med. 2018;20(11):1324-7. [PMID: 29493579]
92) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer Early Detection Version 2. 2024.
93) Hanson H, Astiazaran-Symonds E, Amendola LM, et al. Management of individuals with germline pathogenic/likely pathogenic variants in CHEK2: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2023;25(10):100870. [PMID: 37490054]
94) Mirshahi UL, Kim J, Best AF, et al. A Genome-First Approach to Characterize DICER1 Pathogenic Variant Prevalence, Penetrance, and Phenotype. JAMA Netw Open. 2021;4(2):e210112. [PMID: 33630087]
95) Kim J, Field A, Schultz KAP, et al. The prevalence of DICER1 pathogenic variation in population databases. Int J Cancer. 2017;141(10):2030-6. [PMID: 28748527]

96) Stewart DR, Best AF, Williams GM, et al. Neoplasm Risk Among Individuals With a Pathogenic Germline Variant in DICER1. J Clin Oncol. 2019;37(8):668-76. [PMID: 30715996]
97) Schultz KAP, Harris AK, Finch M, et al. DICER1-related Sertoli-Leydig cell tumor and gynandroblastoma: Clinical and genetic findings from the International Ovarian and Testicular Stromal Tumor Registry. Gynecol Oncol. 2017;147(3):521-7. [PMID: 29037807]
98) Khan NE, Bauer AJ, Schultz KAP, et al. Quantification of Thyroid Cancer and Multinodular Goiter Risk in the DICER1 Syndrome: A Family-Based Cohort Study. J Clin Endocrinol Metab. 2017; 102(5):1614-22. [PMID: 28323992]
99) Huryn LA, Turriff A, Harney LA, et al. DICER1 Syndrome: Characterization of the Ocular Phenotype in a Family-Based Cohort Study. Ophthalmology. 2019;126(2):296-304. [PMID: 30339877]
100) Schultz KAP, Williams GM, Kamihara J, et al. DICER1 and Associated Conditions: Identification of At-risk Individuals and Recommended Surveillance Strategies. Clin Cancer Res. 2018;24(10): 2251-61. [PMID: 29343557]
101) Bakhuizen JJ, Hanson H, van der Tuin K, et al. Surveillance recommendations for DICER1 pathogenic variant carriers: a report from the SIOPE Host Genome Working Group and CanGene-CanVar Clinical Guideline Working Group. Fam Cancer. 2021;20(4):337-48. [PMID: 34170462]
102) Koelsche C, Mynarek M, Schrimpf D, et al. Primary intracranial spindle cell sarcoma with rhabdomyosarcoma-like features share a highly distinct methylation profile and DICER1 mutations. Acta Neuropathol. 2018;136(2):327-37. [PMID: 29881993]
103) Messinger YH, Stewart DR, Priest JR, et al. Pleuropulmonary blastoma: a report on 350 central pathology-confirmed pleuropulmonary blastoma cases by the International Pleuropulmonary Blastoma Registry. Cancer. 2015;121(2):276-85. [PMID: 25209242]
104) Fujita M, Abe K, Kuroda H, et al. Influence of skeletal muscle volume loss during lenvatinib treatment on prognosis in unresectable hepatocellular carcinoma: a multicenter study in Tohoku, Japan. Sci Rep. 2022;12(1):6479. [PMID: 35444161]
105) Kempers MJ, Kuiper RP, Ockeloen CW, et al. Risk of colorectal and endometrial cancers in EPCAM deletion-positive Lynch syndrome: a cohort study. Lancet Oncol. 2011;12(1):49-55. [PMID: 21145788]
106) Wimmer K, Kratz CP, Vasen HF, et al.; EU-Consortium Care for CMMRD (C4CMMRD). Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). J Med Genet. 2014;51(6):355-65 [PMID: 24737826]
107) Hasumi H, Yao M. Hereditary kidney cancer syndromes: Genetic disorders driven by alterations in metabolism and epigenome regulation. Cancer Sci. 2018;109(3):581-6. [PMID: 29325224]

108) Vocke CD, Ricketts CJ, Merino MJ, et al. Comprehensive genomic and phenotypic characterization of germline FH deletion in hereditary leiomyomatosis and renal cell carcinoma. Genes Chromosomes Cancer. 2017;56(6):484-92. [PMID: 28196407]
109) Muller M, Ferlicot S, Guillaud-Bataille M, et al. Reassessing the clinical spectrum associated with hereditary leiomyomatosis and renal cell carcinoma syndrome in French FH mutation carriers. Clin Genet. 2017;92(6):606-15. [PMID: 28300276]
110) Kamihara J, Schultz KA, Rana HQ. FH Tumor Predisposition Syndrome. Adam MP, Feldman J, Mirzaa GM, et al (eds). GeneReviews® [Internet], Seattle (WA): University of Washington Jul 31, 2006 [Last revision: Aug 13, 2020]
https://www.ncbi.nlm.nih.gov/books/NBK1252/
111) Hasumi H and Yao M. [Tumor syndromes] [Chapter 5] Hereditary Renal Tumors, CLINICAL Findings: Hereditary Leiomyomatosis And Renal Cell Carcinoma (HLRCC) Syndrome. Clinical Imaging. 2015; 31 (October Special Issue): 179-82.
112) Jikuya R, Murakami K, Nishiyama A, et al. Single-cell transcriptomes underscore genetically distinct tumor characteristics and microenvironment for hereditary kidney cancers. iScience. 2022;25(6):104463. [PMID: 35874919]
113) Hasumi H, Baba M, Hasumi Y, et al. Birt-Hogg-Dube syndrome: Clinical and molecular aspects of recently identified kidney cancer syndrome. Int J Urol. 2016;23(3):204-10 [PMID: 26608100]
114) Isono Y, Furuya M, Kuwahara T, et al. FLCN alteration drives metabolic reprogramming towards nucleotide synthesis and cyst formation in salivary gland. Biochem Biophys Res Commun. 2020; 522(4):931-8. [PMID: 31806376]
115) Guda K, Moinova H, He J, et al. Inactivating germ-line and somatic mutations in polypeptide N-acetylgalactosaminyltransferase 12 in human colon cancers. Proc Natl Acad Sci U S A. 2009; 106(31):12921-5. [PMID: 19617566]
116) Evans DR, Venkitachalam S, Revoredo L, et al. Evidence for GALNT12 as a moderate penetrance gene for colorectal cancer. Hum Mutat. 2018;39(8):1092-101. [PMID: 29749045]
117) Clarke E, Green RC, Green JS, et al. Inherited deleterious variants in GALNT12 are associated with CRC susceptibility. Hum Mutat. 2012;33(7):1056-8. [PMID: 22461326]
118) Rozen P, Samuel Z, Brazowski E. A prospective study of the clinical, genetic, screening, and pathologic features of a family with hereditary mixed polyposis syndrome. Am J Gastroenterol. 2003;98(10):2317-20. [PMID: 14572586]
119) Lieberman S, Walsh T, Schechter M, et al. Features of Patients With Hereditary Mixed Polyposis Syndrome Caused by Duplication of GREM1 and Implications for Screening and Surveillance. Gastroenterology. 2017;152(8):1876-80. e1. [PMID: 28242209]
120) Ewing CM, Ray AM, Lange EM, et al. Germline mutations in HOXB13 and prostate-cancer risk. N Engl J Med. 2012;366(2):141-9. [PMID: 22236224]

121) Giri VN, Knudsen KE, Kelly WK, et al. Implementation of Germline Testing for Prostate Cancer: Philadelphia Prostate Cancer Consensus Conference 2019. J Clin Oncol. 2020;38(24):2798-811. [PMID: 32516092]
122) Lin X, Qu L, Chen Z, et al. A novel germline mutation in HOXB13 is associated with prostate cancer risk in Chinese men. Prostate. 2013;73(2):169-75. [PMID: 22718278]
123) Kote-Jarai Z, Mikropoulos C, Leongamornlert DA, et al; UK Genetic Prostate Cancer Study Collaborators, and the ProtecT Study Group. Prevalence of the HOXB13 G84E germline mutation in British men and correlation with prostate cancer risk, tumour characteristics and clinical outcomes. Ann Oncol. 2015;26(4):756-61. [PMID: 25595936]
124) Burnichon N, Cascón A, Schiavi F, et al. MAX mutations cause hereditary and sporadic pheochromocytoma and paraganglioma. Clin Cancer Res. 2012;18(10):2828-37. [PMID: 22452945]
125) The Japan Endocrine Society. Clinical Practice Guidelines for Pheochromocytoma and Paraganglioma, 2018 Edition. Shindan To Chiryo Sha, Inc., 2018.
126) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Neuroendocrine and Adrenal Tumors Version 1. 2024.
127) Nölting S, Bechmann N, Taieb D, et al. Personalized Management of Pheochromocytoma and Paraganglioma. Endocr Rev. 2022;43(2):199-239. [PMID: 34147030]
128) Seabrook AJ, Harris JE, Velosa SB, et al. Multiple Endocrine Tumors Associated with Germline MAX Mutations: Multiple Endocrine Neoplasia Type 5? J Clin Endocrinol Metab. 2021;106(4): 1163-82. [PMID: 33367756]
129) Taïeb D, Jha A, Guerin C, et al. 18F-FDOPA PET/CT Imaging of MAX-Related Pheochromocytoma. J Clin Endocrinol Metab. 2018;103(4):1574-82. [PMID: 29534198]
130) Sakurai A, Suzuki S, Kosugi S, et al. Multiple endocrine neoplasia type 1 in Japan: establishment and analysis of a multicentre database. Clin Endocrinol (Oxf). 2012;76(4):533-9. [PMID: 21950691]
131) de Laat JM, van der Luijt RB, Pieterman CR, et al. MEN1 redefined, a clinical comparison of mutation-positive and mutation-negative patients. BMC Med. 2016;14(1):182 [PMID: 27842554]
132) Romanet P, Mohamed A, Giraud S, et al. UMD-MEN1 Database: An Overview of the 370 MEN1 Variants Present in 1676 Patients From the French Population. J Clin Endocrinol Metab. 2019; 104(3):753-64. [PMID: 30339208]
133) de Laat JM, Dekkers OM, Pieterman CR, et al. Long-Term Natural Course of Pituitary Tumors in Patients With MEN1: Results From the DutchMEN1 Study Group (DMSG). J Clin Endocrinol Metab. 2015;100(9):3288-96. [PMID: 26126205]
134) Pieterman CRC, Valk GD. Update on the clinical management of multiple endocrine neoplasia type 1. Clin Endocrinol (Oxf). 2022;97(4):409-23. [PMID: 35319130]
135) Editorial Committee for Guidebook for Management of Multiple Endocrine Neoplasia (ed.). Guidebook for Management of Multiple Endocrine Neoplasia. Kanehara Publishing Co., Ltd. 2013.

136) Japan NeuroEndocrine Tumor Society (JNETS) (ed.). Clinical Practice Guidelines for Pancreatic and Gastrointestinal Neuroendocrine Neoplasia (NEN), 2019 Edition, 2nd Edition. Kanehara Publishing Co., Ltd. 2019.
137) Thakker RV, Newey PJ, Walls GV, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab. 2012;97(9):2990-3011. [PMID: 22723327]
138) Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab. 2001;86(12):5658-71. [PMID: 11739416]
139) Manoharan J, Raue F, Lopez CL, et al. Is Routine Screening of Young Asymptomatic MEN1 Patients Necessary? World J Surg. 2017;41(8):2026-32. [PMID: 28321559]
140) Marini F, Falchetti A, Del Monte F, et al. Multiple endocrine neoplasia type 1. Orphanet J Rare Dis. 2006;1:38. [PMID: 17014705]
141) Schmidt L, Junker K, Weirich G, et al. Two North American families with hereditary papillary renal carcinoma and identical novel mutations in the MET proto-oncogene. Cancer Res. 1998;58(8):1719-22. [PMID: 9563489]
142) Schmidt LS, Nickerson ML, Angeloni D, et al. Early onset hereditary papillary renal carcinoma: germline missense mutations in the tyrosine kinase domain of the met proto-oncogene. J Urol. 2004;172(4 Pt 1):1256-61. [PMID: 15371818]
143) Win AK, Jenkins MA, Dowty JG, et al. Prevalence and Penetrance of Major Genes and Polygenes for Colorectal Cancer. Cancer Epidemiol Biomarkers Prev. 2017;26(3):404-12 [PMID: 27799157]
144) Bonadona V, Bonaïti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA. 2011;305(22):2304-10. [PMID: 21642682]
145) Møller P, Seppälä TT, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. Gut. 2018;67(7):1306-16. [PMID: 28754778]
146) Ryan NAJ, Morris J, Green K, et al. Association of Mismatch Repair Mutation With Age at Cancer Onset in Lynch Syndrome: Implications for Stratified Surveillance Strategies. JAMA Oncol. 2017;3(12):1702-6. [PMID: 28772289]
147) Engel C, Loeffler M, Steinke V, et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. J Clin Oncol. 2012;30(35):4409-15. [PMID: 23091106]
148) Joost P, Therkildsen C, Dominguez-Valentin M, et al. Urinary Tract Cancer in Lynch Syndrome; Increased Risk in Carriers of MSH2 Mutations. Urology. 2015;86(6):1212-7 [PMID: 26385421]
149) Stjepanovic N, Moreira L, Carneiro F, et al.; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Hereditary gastrointestinal cancers: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019;30(10):1558-71. [PMID: 31378807]

150) Monahan KJ, Bradshaw N, Dolwani S, et al.; Hereditary CRC guidelines eDelphi consensus group. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). Gut. 2020;69(3):411-44 [PMID: 31780574]

151) Giardiello FM, Allen JI, Axilbund JE, et al.; US Multi-Society Task Force on Colorectal Cancer. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on colorectal cancer. Gastroenterology. 2014;147(2):502-26. [PMID: 25043945]

152) Dominguez-Valentin M, Sampson JR, Seppälä TT, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. Genet Med. 2020;22(1):15-25. [PMID: 31337882]

153) Salo-Mullen EE, Maio A, Mukherjee S, et al. Prevalence and Characterization of Biallelic and Monoallelic NTHL1 and MSH3 Variant Carriers From a Pan-Cancer Patient Population. JCO Precis Oncol. 2021;5:PO.20.00443. [PMID: 34250384]

154) Adam R, Spier I, Zhao B, et al. Exome Sequencing Identifies Biallelic MSH3 Germline Mutations as a Recessive Subtype of Colorectal Adenomatous Polyposis. Am J Hum Genet. 2016;99(2): 337-51. [PMID: 27476653]

155) Suerink M, Rodríguez-Girondo M, van der Klift HM, et al. An alternative approach to establishing unbiased colorectal cancer risk estimation in Lynch syndrome. Genet Med. 2019;21(12):2706-12. [PMID: 31204389]

156) Baglietto L, Lindor NM, Dowty JG, et al. Risks of Lynch syndrome cancers for MSH6 mutation carriers. J Natl Cancer Inst. 2010;102(3):193-201. [PMID: 20028993]

157) van Leerdam ME, Roos VH, van Hooft JE, et al. Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2019;51(9): 877-95. [PMID: 31342472]

158) Yang J, Gurudu SR, Koptiuch C, et al. American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in familial adenomatous polyposis syndromes. Gastrointest Endosc. 2020; 91(5):963-82. e2. [PMID: 32169282]

159) Lubbe SJ, Di Bernardo MC, Chandler IP, et al. Clinical implications of the colorectal cancer risk associated with MUTYH mutation. J Clin Oncol. 2009;27(24):3975-80. [PMID: 19620482]

160) Vogt S, Jones N, Christian D, et al. Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. Gastroenterology. 2009;137(6):1976-85. e1-10. [PMID: 19732775]

161) Grover S, Kastrinos F, Steyerberg EW, et al. Prevalence and phenotypes of APC and MUTYH mutations in patients with multiple colorectal adenomas. JAMA. 2012;308(5):485-92. [PMID: 22851115]

162) Kallionpää RA, Uusitalo E, Leppävirta J, et al. Prevalence of neurofibromatosis type 1 in the Finnish population. Genet Med. 2018;20(9):1082-6. [PMID: 29215653]
163) Yoshida Y, Kuramochi A, Ota A, et al. Revision Committee for Clinical Practice Guidelines for Neurofibromatosis Type 1. Clinical Practice Guidelines for Neurofibromatosis Type 1 (von Recklinghausen disease), 2018 Edition. The Journal of Dermatology. 2018; 128(1): 17-34.
164) Japan Society for Neuro-Oncology (ed.). Clinical Practice Guidelines for Brain Tumor: Pediatric Brain Tumor, 2021 Edition. Kanehara Publishing Co., Ltd. 2021.
165) Creation Committee for Clinical Practice Guidelines for Plexiform Neurofibroma-Malignant Peripheral Nerve Sheath Tumor (ed.). Clinical Practice Guidelines for Plexiform Neurofibroma-Malignant Peripheral Nerve Sheath Tumor. Igakutosho Shuppan, 2024.
166) Miller DT, Freedenberg D, Schorry E, et al. Health Supervision for Children With Neurofibromatosis Type 1. Pediatrics. 2019;143(5):e20190660. [PMID: 31010905]
167) Takagi H. Overlap rate and nationwide number of patients in the secondary survey of von Recklinghausen disease and tuberous sclerosis. The 1987 Research Report of the Ministry of Health, Labour and Welfare Designated Disease: Survey Research on Neurocutaneous Syndromes. 1988. pp. 169-170.
168) Mussi C, Schildhaus HU, Gronchi A, et al. Therapeutic consequences from molecular biology for gastrointestinal stromal tumor patients affected by neurofibromatosis type 1. Clin Cancer Res. 2008;14(14):4550-5. [PMID: 18628470]
169) Takano T, Kawashima T, Yamanouchi Y, et al. Genetics of neurofibromatosis 1 in Japan: mutation rate and paternal age effect. Hum Genet. 1992;89(3):281-6. [PMID: 1351032]
170) Evans DG, Bowers NL, Tobi S, et al. Schwannomatosis: a genetic and epidemiological study. J Neurol Neurosurg Psychiatry. 2018;89(11):1215-9. [PMID: 29909380]
171) Forde C, King AT, Rutherford SA, et al. Disease course of neurofibromatosis type 2: a 30-year follow-up study of 353 patients seen at a single institution. Neuro Oncol. 2021;23(7):1113-24. [PMID: 33336705]
172) Mautner VF, Lindenau M, Baser ME, et al. The neuroimaging and clinical spectrum of neurofibromatosis 2. Neurosurgery. 1996;38(5):880-5;discussion 885-6. [PMID: 8727812]
173) Smith MJ, Higgs JE, Bowers NL, et al. Cranial meningiomas in 411 neurofibromatosis type 2(NF2) patients with proven gene mutations: clear positional effect of mutations, but absence of female severity effect on age at onset. J Med Genet. 2011;48(4):261-5. [PMID: 21278391]
174) Mautner VF, Lindenau M, Baser ME, et al. Skin abnormalities in neurofibromatosis 2. Arch Dermatol. 1997;133(12):1539-43. [PMID: 9420538]
175) Research Group on Neurocutaneous Syndromes. Treatment Guidelines for Neurofibromatosis Type 2 (Revised October 2016). 2016.
https://plaza.umin.ac.jp/nf2guideline/shishin.html

176) Halliday D, Emmanouil B, Evans DGR. Updated protocol for genetic testing, screening and clinical management of individuals at risk of NF2-related schwannomatosis. Clin Genet. 2023;103(5): 540-52. [PMID: 36762955]
177) Weren RD, Ligtenberg MJ, Kets CM, et al. A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer. Nat Genet. 2015;47 (6):668-71. [PMID: 25938944]
178) Weren RD, Ligtenberg MJ, Geurts van Kessel A, et al. NTHL1 and MUTYH polyposis syndromes: two sides of the same coin? J Pathol. 2018;244(2):135-42. [PMID: 29105096]
179) Beck SH, Jelsig AM, Yassin HM, et al. Intestinal and extraintestinal neoplasms in patients with NTHL1 tumor syndrome: a systematic review. Fam Cancer. 2022;21(4):453-62. [PMID: 35292903]
180) Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med. 2014;371(6):497-06. [PMID: 25099575]
181) Yang X, Leslie G, Doroszuk A, et al. Cancer Risks Associated With Germline PALB2 Pathogenic Variants: An International Study of 524 Families. J Clin Oncol. 2020;38(7):674-85. [PMID: 31841383]
182) Ten Broeke SW, van der Klift HM, Tops CMJ, et al. Cancer Risks for PMS2-Associated Lynch Syndrome. J Clin Oncol. 2018;36(29):2961-8. [PMID: 30161022]
183) Senter L, Clendenning M, Sotamaa K, et al. The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology. 2008;135(2):419-28. [PMID: 18602922]
184) Buchanan DD, Stewart JR, Clendenning M, et al. Risk of colorectal cancer for carriers of a germ-line mutation in POLE or POLD1. Genet Med. 2018;20(8):890-5. [PMID: 29120461]
185) Palles C, Martin L, Domingo E, et al. The clinical features of polymerase proof-reading associated polyposis (PPAP) and recommendations for patient management. Fam Cancer. 2022;21(2): 197-209. [PMID: 33948826]
186) Valle L, Hernández-Illán E, Bellido F, et al. New insights into POLE and POLD1 germline mutations in familial colorectal cancer and polyposis. Hum Mol Genet. 2014;23(13):3506-12. [PMID: 24501277]
187) Palles C, Cazier JB, Howarth KM, et al. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat Genet. 2013;45 (2):136-44. [PMID: 23263490]
188) Robinson PS, Coorens THH, Palles C, et al. Increased somatic mutation burdens in normal human cells due to defective DNA polymerases. Nat Genet. 2021;53(10):1434-42.
189) Aoude LG, Heitzer E, Johansson P, et al. POLE mutations in families predisposed to cutaneous melanoma. Fam Cancer. 2015;14(4):621-8. [PMID: 26251183]
190) Hansen MF, Johansen J, Bjørnevoll I, et al. A novel POLE mutation associated with cancers of colon, pancreas, ovaries and small intestine. Fam Cancer. 2015;14(3):437-48 [PMID: 25860647]

191) Spier I, Holzapfel S, Altmüller J, et al. Frequency and phenotypic spectrum of germline mutations in POLE and seven other polymerase genes in 266 patients with colorectal adenomas and carcinomas. Int J Cancer. 2015;137(2):320-31. [PMID: 25529843]
192) Rohlin A, Zagoras T, Nilsson S, et al. A mutation in POLE predisposing to a multi-tumour phenotype. Int J Oncol. 2014;45(1):77-81. [PMID: 24788313]
193) Mur P, García-Mulero S, Del Valle J, et al. Role of POLE and POLD1 in familial cancer. Genet Med. 2020;22(12):2089-100. [PMID: 32792570]
194) Tan MH, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res. 2012;18(2):400-7. [PMID: 22252256]
195) Takayama T, Igarashi M, Ohsumi S, et al. Clinical Practice Guidelines for Cowden Syndrome/*PTEN* Hamartoma Tumor Syndrome in Children and Adults (2020 Edition). Journal of Hereditary Tumors. 2020;20(2):93-114.
196) Song H, Dicks E, Ramus SJ, et al. Contribution of Germline Mutations in the RAD51B, RAD51C, and RAD51D Genes to Ovarian Cancer in the Population. J Clin Oncol. 2015;33(26):2901-7. [PMID: 26261251]
197) Yang X, Song H, Leslie G, et al. Ovarian and Breast Cancer Risks Associated With Pathogenic Variants in RAD51C and RAD51D. J Natl Cancer Inst. 2020;112(12):1242-50 [PMID: 32107557]
198) Harbour JW. Molecular basis of low-penetrance retinoblastoma. Arch Ophthalmol. 2001;119(11):1699-704. [PMID: 11709023]
199) Alekseeva EA, Babenko OV, Kozlova VM, et al. Parental Origin of the RB1 Gene Mutations in Families with Low Penetrance Hereditary Retinoblastoma. Cancers (Basel). 2021;13(20):5068. [PMID: 34680218]
200) Reddy MA, Butt M, Hinds AM, et al. Prognostic Information for Known Genetic Carriers of RB1 Pathogenic Variants (Germline and Mosaic). Ophthalmol Retina. 2021;5(4):381-7. [PMID: 32835838]
201) The Japanese Society of Pediatric Hematology/Oncology (ed.). Clinical Practice Guidelines for Pediatric Cancer, 2016 Edition. Kanehara Publishing Co., Ltd. 2016.
202) Kamihara J, Bourdeaut F, Foulkes WD, et al. Retinoblastoma and Neuroblastoma Predisposition and Surveillance. Clin Cancer Res. 2017;23(13):e98-106. [PMID: 28674118]
203) Skalet AH, Gombos DS, Gallie BL, et al. Screening Children at Risk for Retinoblastoma: Consensus Report from the American Association of Ophthalmic Oncologists and Pathologists. Ophthalmology. 2018;125(3):453-8. [PMID: 29056300]
204) Committee for the National Registry of Retinoblastoma. The National Registry of Retinoblastoma in Japan (1983-2014). Jpn J Ophthalmol. 2018;62(4):409-23. [PMID: 29846838]
205) Skinner MA, Moley JA, Dilley WG, et al. Prophylactic thyroidectomy in multiple endocrine neoplasia type 2A. N Engl J Med. 2005;353(11):1105-13. [PMID: 16162881]

206) Casanova S, Rosenberg-Bourgin M, Farkas D, et al. Phaeochromocytoma in multiple endocrine neoplasia type 2A: survey of 100 cases. Clin Endocrinol (Oxf). 1993;38(5):531-7. [PMID: 8101147]
207) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Thyroid Carcinoma. Version 2. 2024.
208) Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25(6):567-610 [PMID: 25810047]
209) Marini F, Falchetti A, Del Monte F, et al. Multiple endocrine neoplasia type 2. Orphanet J Rare Dis. 2006;1:45. [PMID: 17105651]
210) Mathiesen JS, Kroustrup JP, Vestergaard P, et al. Incidence and prevalence of multiple endocrine neoplasia 2A in Denmark 1901-2014: a nationwide study. Clin Epidemiol. 2018;10:1479-87. [PMID: 30349395]
211) Garutti M, Foffano L, Mazzeo R, et al. Hereditary Cancer Syndromes: A Comprehensive Review with a Visual Tool. Genes (Basel). 2023;14(5):1025. [PMID: 37239385]
212) Benn DE, Zhu Y, Andrews KA, et al. Bayesian approach to determining penetrance of pathogenic SDH variants. J Med Genet. 2018;55(11):729-34. [PMID: 30201732]
213) Hanson H, Durkie M, Lalloo F, et al. UK recommendations for SDHA germline genetic testing and surveillance in clinical practice. J Med Genet. 2023;60(2):107-11. [PMID: 35260474]
214) Amar L, Pacak K, Steichen O, et al. International consensus on initial screening and follow-up of asymptomatic SDHx mutation carriers. Nat Rev Endocrinol. 2021;17(7):435-44. [PMID: 34021277]
215) Kunst HP, Rutten MH, de Mönnink JP, et al. SDHAF2 (PGL2-SDH5) and hereditary head and neck paraganglioma. Clin Cancer Res. 2011;17(2):247-54. [PMID: 21224366]
216) Muth A, Crona J, Gimm O, et al. Genetic testing and surveillance guidelines in hereditary pheochromocytoma and paraganglioma. J Intern Med. 2019;285(2):187-204. [PMID: 30536464]
217) Bayley JP, Kunst HP, Cascon A, et al. SDHAF2 mutations in familial and sporadic paraganglioma and phaeochromocytoma. Lancet Oncol. 2010;11(4):366-72. [PMID: 20071235]
218) Hao HX, Khalimonchuk O, Schraders M, et al. SDH5, a gene required for flavination of succinate dehydrogenase, is mutated in paraganglioma. Science. 2009;325(5944):1139-42. [PMID: 19628817]
219) Andrews KA, Ascher DB, Pires DEV, et al. Tumour risks and genotype-phenotype correlations associated with germline variants in succinate dehydrogenase subunit genes SDHB, SDHC and SDHD. J Med Genet. 2018;55(6):384-94. [PMID: 29386252]
220) Davidoff DF, Benn DE, Field M, et al. Surveillance Improves Outcomes for Carriers of SDHB Pathogenic Variants: A Multicenter Study. J Clin Endocrinol Metab. 2022;107(5):e1907-16. [PMID: 35037935]
221) Greenberg SE, Jacobs MF, Wachtel H, et al. Tumor detection rates in screening of individuals with SDHx-related hereditary paraganglioma-pheochromocytoma syndrome. Genet Med. 2020; 22(12):2101-7. [PMID: 32741965]

222) Saie C, Buffet A, Abeillon J, et al. Screening of a Large Cohort of Asymptomatic SDHx Mutation Carriers in Routine Practice. J Clin Endocrinol Metab. 2021;106(3):e1301-15 [PMID: 33247927]
223) Williams ST, Chatzikyriakou P, Carroll PV, et al. SDHC phaeochromocytoma and paraganglioma: A UK-wide case series. Clin Endocrinol (Oxf). 2022;96(4):499-512. [PMID: 34558728]
224) Taïeb D, Wanna GB, Ahmad M, et al. Clinical consensus guideline on the management of phaeochromocytoma and paraganglioma in patients harbouring germline SDHD pathogenic variants. Lancet Diabetes Endocrinol. 2023;11(5):345-361. [PMID: 37011647]
225) Burnichon N, Mazzella JM, Drui D, et al. Risk assessment of maternally inherited SDHD paraganglioma and phaeochromocytoma. J Med Genet. 2017;54(2):125-33. [PMID: 27856506]
226) O'Malley M, LaGuardia L, Kalady MF, et al. The prevalence of hereditary hemorrhagic telangiectasia in juvenile polyposis syndrome. Dis Colon Rectum. 2012;55(8):886-92. [PMID: 22810475]
227) Schwenter F, Faughnan ME, Gradinger AB, et al. Juvenile polyposis, hereditary hemorrhagic telangiectasia, and early onset colorectal cancer in patients with SMAD4 mutation. J Gastroenterol. 2012;47(7):795-804. [PMID: 22331366]
228) Ishida H, Tajima Y, Gonda T, et al. Update on our investigation of malignant tumors associated with Peutz-Jeghers syndrome in Japan. Surg Today. 2016;46(11):1231-42 [PMID: 26746637]
229) Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology. 2000;119(6):1447-53. [PMID: 11113065]
230) Yamamoto H, Abe T, Ishiguro S, et al. Clinical Practice Guidelines for Peutz-Jeghers Syndrome in Children and Adults (2020 Edition). Journal of Hereditary Tumors. 2020;20(2):59-78.
231) Wu BD, Wang YJ, Fan LL, et al. Clinical and Genetic Analyses of 38 Chinese Patients with Peutz-Jeghers Syndrome. Biomed Res Int. 2020;2020:9159315. [PMID: 32462036]
232) Toledo SP, Lourenço DM, Jr., Sekiya T, et al. Penetrance and clinical features of pheochromocytoma in a six-generation family carrying a germline TMEM127 mutation. J Clin Endocrinol Metab. 2015;100(2):E308-18. [PMID: 25389632]
233) Armaiz-Pena G, Flores SK, Cheng ZM, et al. Genotype-Phenotype Features of Germline Variants of the TMEM127 Pheochromocytoma Susceptibility Gene: A 10-Year Update. J Clin Endocrinol Metab. 2021;106(1):e350-64. [PMID: 33051659]
234) de Andrade KC, Mirabello L, Stewart DR, et al. Higher-than-expected population prevalence of potentially pathogenic germline TP53 variants in individuals unselected for cancer history. Hum Mutat. 2017;38(12):1723-30. PMID: 28861920
235) de Andrade KC, Strande NT, Kim J, et al. Genome-first approach of the prevalence and cancer phenotypes of pathogenic or likely pathogenic germline TP53 variants. HGG Adv. 2024;5(1): 100242. [PMID: 37777824]

236) Gonzalez KD, Noltner KA, Buzin CH, et al. Beyond Li Fraumeni Syndrome: clinical characteristics of families with p53 germline mutations. J Clin Oncol. 2009;27(8):1250-6. [PMID: 19204208]
237) McBride KA, Ballinger ML, Killick E, et al. Li-Fraumeni syndrome: cancer risk assessment and clinical management. Nat Rev Clin Oncol. 2014;11(5):260-71. [PMID: 24642672]
238) Bougeard G, Renaux-Petel M, Flaman JM, et al. Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers. J Clin Oncol. 2015;33(21):2345-52. [PMID: 26014290]
239) Mai PL, Best AF, Peters JA, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. Cancer. 2016;122(23): 3673-81. [PMID: 27496084]
240) Research Group for the Implementation of Genomic Medicine System for Hereditary Tumors Occurring in Childhood (ed.). Clinical Practice Guidelines for Li-Fraumeni Syndrome, 2019 Edition. 2019 Fiscal Year Edition ver. 1.1. https://www.jspho.org/pdf/journal/li-fraumeni/li-fraumeni_1.pdf
241) Frebourg T, Bajalica Lagercrantz S, Oliveira C, et al. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes. Eur J Hum Genet. 2020;28(10):1379-86. [PMID: 32457520]
242) Hanson H, Brady AF, Crawford G, et al. UKCGG Consensus Group guidelines for the management of patients with constitutional TP53 pathogenic variants. J Med Genet. 2020;58(2):135-9.
243) Sánchez-Heras AB, Ramon Y Cajal T, Pineda M, et al. SEOM clinical guideline on heritable TP53-related cancer syndrome (2022). Clin Transl Oncol. 2023;25(9):2627-33 [PMID: 37133731]
244) Kaneda M, Mizuguchi M, Hatano T, et al. Committee for the Revision of “Diagnostic Criteria and Treatment Guidelines for Tuberous Sclerosis.” Japanese Dermatological Association Guidelines, Diagnostic Criteria and Treatment Guidelines for Tuberous Sclerosis, Revised Edition. The Journal of Dermatology. 2018; 128(1): 1-16.
245) Japanese Urological Association and Japanese Society of Tuberous Sclerosis Complex (ed.). Clinical Practice Guidelines for Renal Angiomyolipoma Associated with Tuberous Sclerosis, 2016 Edition. Medical View Co., 2016.
246) Northrup H, Aronow ME, Bebin EM, et al. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatr Neurol. 2021; 123:50-66. [PMID: 34399110]
247) O’Callaghan FJ, Shiell AW, Osborne JP, et al. Prevalence of tuberous sclerosis estimated by capture-recapture analysis. Lancet. 1998;351(9114):1490. [PMID: 9605811]
248) Ebrahimi-Fakhari D, Mann LL, Poryo M, et al. Incidence of tuberous sclerosis and age at first diagnosis: new data and emerging trends from a national, prospective surveillance study. Orphanet J Rare Dis. 2018;13(1):117. [PMID: 30016967]

249) Sancak O, Nellist M, Goedbloed M, et al. Mutational analysis of the TSC1 and TSC2 genes in a diagnostic setting: genotype--phenotype correlations and comparison of diagnostic DNA techniques in Tuberous Sclerosis Complex. Eur J Hum Genet. 2005;13(6):731-41. [PMID: 15798777]
250) Maher ER, Iselius L, Yates JR, et al. Von Hippel-Lindau disease: a genetic study. J Med Genet. 1991;28(7):443-7. [PMID: 1895313]
251) Group for "Research on the Actual Status and Standardization of Medical Treatment of Hereditary Diseases Causing Various Endocrine Abnormalities (Multiple Endocrine Neoplasia and von Hippel-Lindau Disease)." Clinical Practice Guidelines for von Hippel-Lindau (VHL) Disease, 2017 Edition. 2017.
https://www.kochi-u.ac.jp/kms/hs_urol/pdf/vhl_2017ver.pdf
252) Group for Comprehensive Research on von Hippel-Lindau Disease for the Investigation of the Actual Condition, Establishment of Medical Treatment System, and Improvement of QOL. Clinical Practice Guide for von Hippel-Lindau Disease (2024 Edition). 2024.
https://www.nichigan.or.jp/member/journal/guideline/detail.html?itemid＝716&dispmid＝909
253) Daniels AB, Tirosh A, Huntoon K, et al. Guidelines for surveillance of patients with von Hippel-Lindau disease: Consensus statement of the International VHL Surveillance Guidelines Consortium and VHL Alliance. Cancer. 2023;129(19):2927-40. [PMID: 37337409]
254) Tamura K, Kanazashi Y, Kawada C, et al. Variant spectrum of von Hippel-Lindau disease and its genomic heterogeneity in Japan. Hum Mol Genet. 2023;32(12):2046-54. [PMID: 36905328]
255) Lipska BS, Ranchin B, Iatropoulos P, et al. Genotype-phenotype associations in WT1 glomerulopathy. Kidney Int. 2014;85(5):1169-78. [PMID: 24402088]
256) Lehnhardt A, Karnatz C, Ahlenstiel-Grunow T, et al. Clinical and molecular characterization of patients with heterozygous mutations in wilms tumor suppressor gene 1. Clin J Am Soc Nephrol. 2015;10(5):825-31. [PMID: 25818337]
257) Hol JA, Jewell R, Chowdhury T, et al. Wilms tumour surveillance in at-risk children: Literature review and recommendations from the SIOP-Europe Host Genome Working Group and SIOP Renal Tumour Study Group. Eur J Cancer. 2021;153:51-63. [PMID: 34134020]
258) Lipska-Ziętkiewicz BS. WT1 Disorder. Adam MP, Feldman J, Mirzaa GM, et al (eds). GeneReviews® [Internet], Seattle (WA): University of Washington Apr 30, 2020[Last revision: Apr 29, 2021].
https://www.ncbi.nlm.nih.gov/books/NBK556455/(accessed 2024-08-26)

CHAPTER 5. Materials

1. Family history interview and descriptions of family tree

1. Significance of family history interview and family tree

A detailed interview on family history and the construction of a family tree is valuable for both evaluating genetic health risks and providing psychosocial support.

1. Significance in genetic counseling

For genetic evaluation, the client's clinical information and family history should be organized early in the process of genetic counseling. During genetic counseling sessions, a range of information is examined, including potential hereditary tumor syndromes within the family, options for genetic testing, and identification of individuals who should undergo genetic testing first, based on risk assessment considerations. In some recent cases, family history and genealogical trees have been used as references in tumor-only CGP, which analyzes only tumor tissue, to examine the possibility of germline origin of PGPV upon detection of a pathogenic variant in cancer susceptibility genes.

Furthermore, the process of reviewing family structure and medical history in a family history interview during genetic counseling helps to enhance communication. For example, information obtained during a family history interview may help genetic counselors understand the background of the client, such as family relationships and kinship, residence location of blood relatives, perception and understanding of diseases, and experiences of bereavement and grief. Therefore, a thorough family history interview can be valuable for building rapport and providing psychosocial support.

2. Significance in clinical management

A surveillance plan based on family history may be considered following genetic identification of GPV in the client. Even when considering cancer susceptibility genes that pose a high risk of cancer onset with established medical management guidelines, medical management can be considered on an individual basis, taking into account the characteristic patterns of cancers that have occurred within the family[1)]. Further, genealogical trees are used to identify blood relatives who may share GPV and to consider sharing information with the relatives. Considering the limitations of genetic testing, however, when GPV is not detected, medical management according to individual risks should be considered, taking into account the clinical background with reference to a genealogical tree, based on the limitations of genetic testing.

It is important to note that risk assessment based on family history has limitations. Risk assessment may be difficult due to a lack of information, such as a nuclear family with a small number of members and a lack of sharing of disease information within the family. Additionally, other factors, such as the client's vague memory, may hinder accurate risk assessment. While a detailed family history can be helpful for genetic risk assessment, it should be noted that the absence of a reported family history does not exclude the possibility of hereditary tumor syndromes.

*Rapport: a psychological term referring to the relationship of trust between a genetic counselor and a client.

2. Points to note when collecting information on hereditary cancer syndromes

1. Target range of family tree

When creating a family tree, information related to cancer diagnosis, treatments, and current health status, is usually reviewed using at least three generations as a guide: first-degree relatives (parents, siblings, and children), second-degree relatives (grandparents, uncles, aunts, half-siblings, nephews, nieces, and grandchildren), and third-degree relatives (great-grandparents, great-uncles, great- aunts, cousins, children of nephews and nieces, great-grandchildren, etc.) (Figure 5-1).

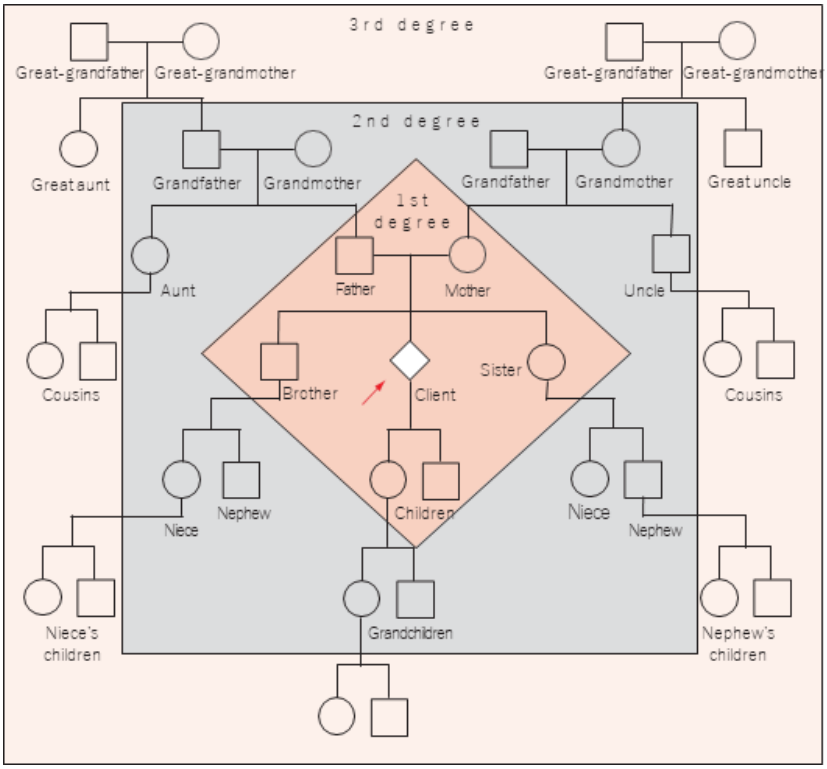


Figure 5-1. Degree of kinship reviewed during family history interview

2. Information collected during family history interview

Information collected for creating a family tree includes the following: family structure centered on the client, the age of family members, and age at death for deceased individuals. For those with a history of cancer, relevant details include the type of cancer and age at diagnosis (with estimated age ranges as helpful references), cancer stage and histological characteristics (such as type and subtype), whether the cancer was single or multiple, unilateral or bilateral, and whether it was a primary or recurrent tumor, as well as details of treatments received. Subsequently, this information is reviewed with consideration of the

characteristics of hereditary cancer syndromes, which may include: (1) cancer onset at a young age, (2) multiple, overlapping, or bilateral cancer, (3) cancer with a distinctive histological type, (4) distinctive physical findings, and (5) rare cancer with low incidence). Since the individual's memory may be inaccurate, it can be desirable to consider devising ways to ask questions, review pathology reports, or request medical information documents depending on the situation. Additionally, a more detailed risk assessment can be made by reviewing genetic testing reports of blood relatives, including the genes analyzed, analysis methods used, and test results, if available.

When conducting a family history interview on blood relatives, the focus is not limited to those with a history of cancer. Information on how long cancer-free individuals lived or remained unaffected by cancer is also essential for assessing genetic risk, as it contributes to a more comprehensive understanding of the overall familial pattern represented in the genealogical tree. Additionally, a review of any cancer-related testing among blood relatives—including the types of tests performed, the timing, and the results—can provide valuable context for risk assessment.

3. Key points of family history interview

There is no fixed rule regarding the order in which information should be collected during a family history interview. However, it is often helpful to begin with the client and gradually expand outward based on degree of kinship, as this approach helps prevent omissions during the review process and makes it easier for the client to organize and recall information (e.g., starting with the client's children, siblings and their children, then moving to the father, paternal uncles and aunts, their children, and paternal grandparents).

Clients often have vague memories of family diseases during medical history interviews. For example, some clients are not able to distinguish between uterine and ovarian cancers, while others remember both uterine body cancer and endocervical cancer as uterine cancer or misunderstand lung metastases as lung cancer.

Additionally, histories of treatment and testing for benign conditions can also be relevant to cancer risk assessment, even in the absence of a cancer diagnosis. For instance, a history of total hysterectomy for uterine fibroids or other benign conditions may indicate a reduced risk of endometrial (uterine body) cancer. Therefore, it is important to collect medical information on blood relatives regardless of whether the disease is benign or malignant.

Some hereditary cancer syndromes may present with distinctive non-tumorous features. For example, when Cowden syndrome or *PTEN* hamartoma tumor syndrome is considered in the differential diagnosis, it is helpful to assess for characteristic dermatological findings and the presence of macrocephaly during the family history interview. In addition, reviewing a history of colonoscopy examination among family members with familial adenomatous polyposis is useful for risk assessment, and it can also provide an opportunity to discuss subsequent health management. Therefore, it is important to conduct a family history interview by selectively collecting necessary information according to the situation of each family.

3. How to create a family tree

A family tree visually represents biological relationships among family members by connecting standardized symbols with lines and includes relevant information such as age and medical history. A family tree is drawn in accordance with the international standard method so that it can be easily understood at a glance by anyone at any time. The standard method was established by the U.S. National Society of Genetic Counselors (NSGC) in 1995 and modified in line with social changes in 2008 and 2022[2-4]. The standard method is also commonly used as a reference in Japan, and it is expected to continue to be the subject of discussion.

***Side note 5-1. Notation of symbols representing individuals based on sex and gender identity**

In light of the diversity of sex, the NSGC redefined the terminology system to distinguish between gender (social sex) and sex (biological sex) in 2022, proposing a method of describing them in genealogical trees[4, 5]. Gender identity involves one's internal sense of self and its conformity to the external world from a gender perspective, and it may or may not match the sex given at birth[4, 5]. Although respect for the gender of clients and patients is a key premise in genetic counseling, the sex given at birth is important information in assessing the risk of cancer onset, prevention, and treatment options. It may also be useful in Japan as a reference for the method of description upon disclosure by clients.

1. Rules for describing symbols that represent individuals (Figures 5-2 and 5-3)

In a genealogical tree, essential information is displayed below the symbols representing individuals, including current age or age at death, age at diagnosis and cancer type (if applicable), and results of genetic testing. Figure 5-4 shows an example of a family tree created based on the definitions and rules of the relationship lines that connect symbols representing individuals. When creating a family tree centered on the client, it is standard practice to place paternal relatives on the left and maternal relatives on the right, which improves clarity and enhances risk assessment visibility. Because each genealogical tree reflects a unique family structure, including a legend for filled or color-coded symbols helps ensure that the information is clearly understood and consistently interpreted.

2. Changes from the traditional method of describing a family tree

In 2022, the NSGC made changes to the traditional method of describing a family tree; it recommended that no dots be used in the center of the symbols that represent heterozygous carriers for AR or XR inheritance diseases, as those notations may cause misunderstandings in actual clinical practice[4, 5]. Among other changes, the notation 'E' (Evaluation) was deleted, and the evaluation results for physical, laboratory, and other findings were placed below the symbols representing individuals[4, 5].

4. Points to note when managing and updating family trees

A genealogical tree is considered the information appropriately stored in medical records and shared among the medical professionals involved in treatment and care. It is managed by clearly indicating the individuals providing information, the date and location of family history interview/update, and the individuals creating the genealogical tree (**Figure 5-4**). As genealogical information, including the occurrence of new cancers, may evolve, previously unconsidered factors may become relevant. For instance, cancer susceptibility genes not initially suspected based on earlier family history may later warrant consideration, especially in light of advances in genetic testing technologies and expanding areas of analysis. Therefore, if the client is currently receiving medical treatment in the hospital, it is recommended that the family history be periodically reviewed during hospital visits. Additionally, clients should be advised to report any new or revised family history information, as such updates may influence risk assessments and management plans.

Although family history is the information that can be shared within a family, careful consideration must be given to the extent to which disease-related information is shared among blood relatives. If a family tree created based on information from the client is subsequently made available to blood relatives when they visit the hospital, it is advisable to inform the client and obtain his/her approval in advance.

Beyond privacy considerations, re-creating a familyl tree centered on each client, even within the same family, can be valuable for risk assessment. For example, as illustrated in Figure 5-4, when the child of an individual diagnosed with hereditary breast and ovarian cancer (HBOC) visits the hospital, it may be appropriate to consider the potential for other hereditary cancer syndromes by evaluating the family line of the other, HBOC-negative, parent from a different perspective. In the familial tree shown, a blood relative of II-3 (III-4) underwent MGPT, and it detected GPV in *MLH1* in addition to *BRCA2*, indicating that the individuals had MINAS (**BQ3 and BQ4 in Chapter 2**) and that Lynch syndrome was of paternal origin. Even if a blood relative visits the hospital for consultation regarding single-site testing, the option of MGPT should also be discussed, if necessary, considering the possible involvement of genetic risk associated with cancer susceptibility genes other than the target variant.

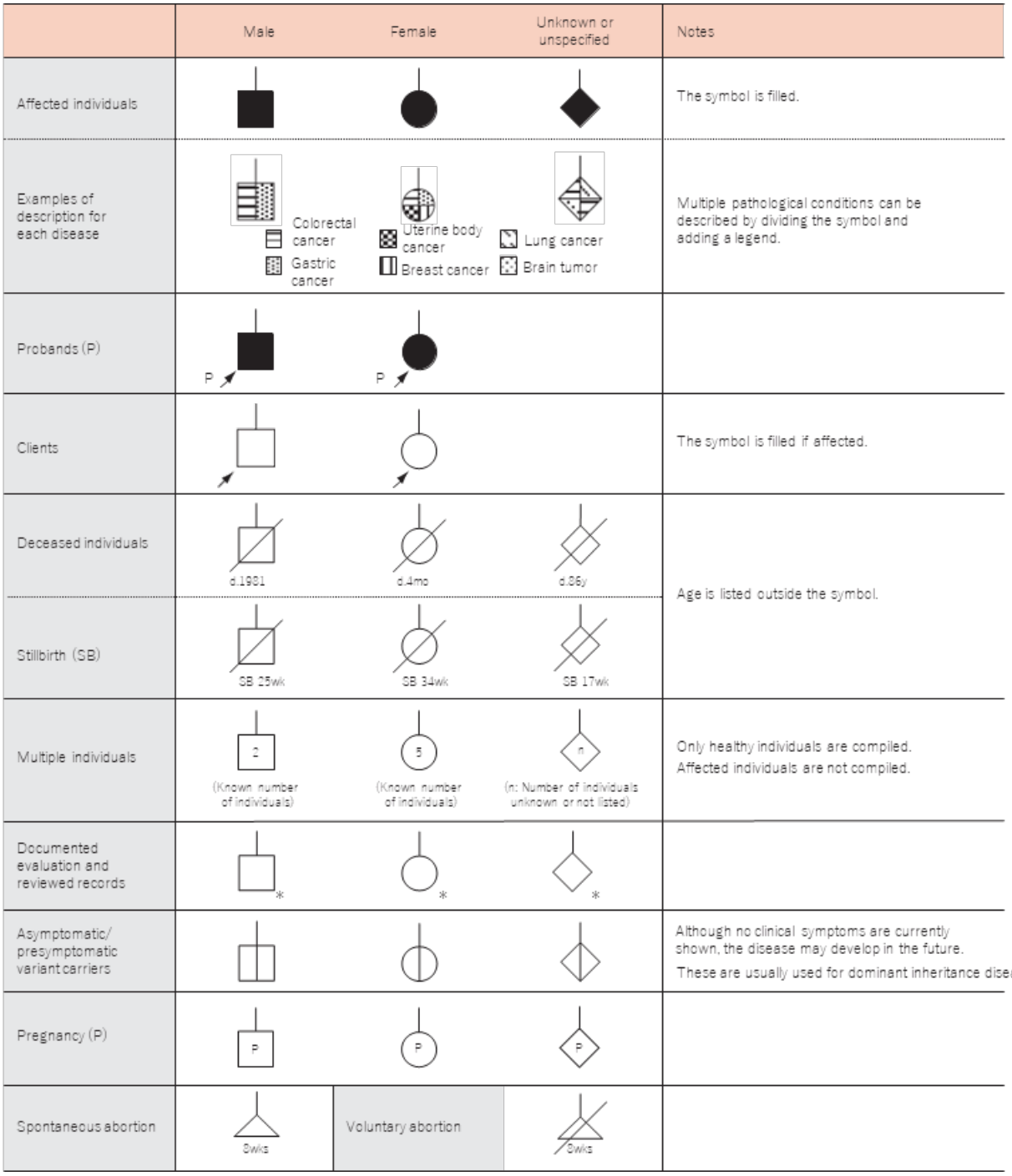


Figure 5-2. Symbols used in family trees

Adapted from "Textbook for Hereditary Tumor Specialists" [6)]

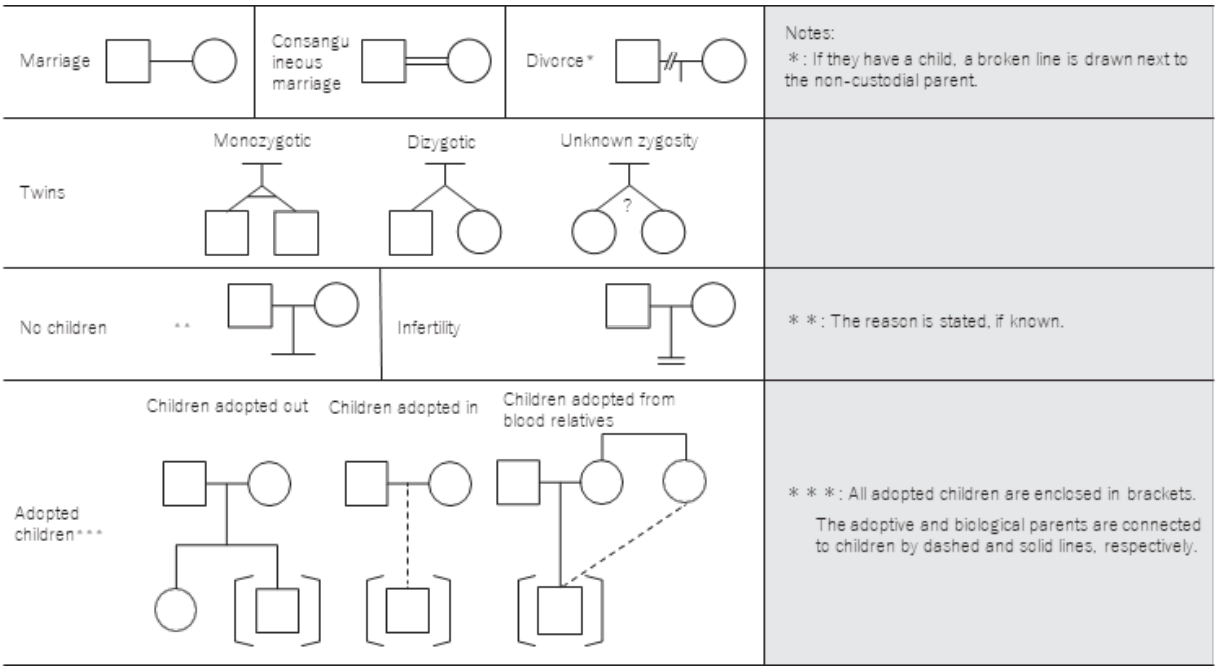
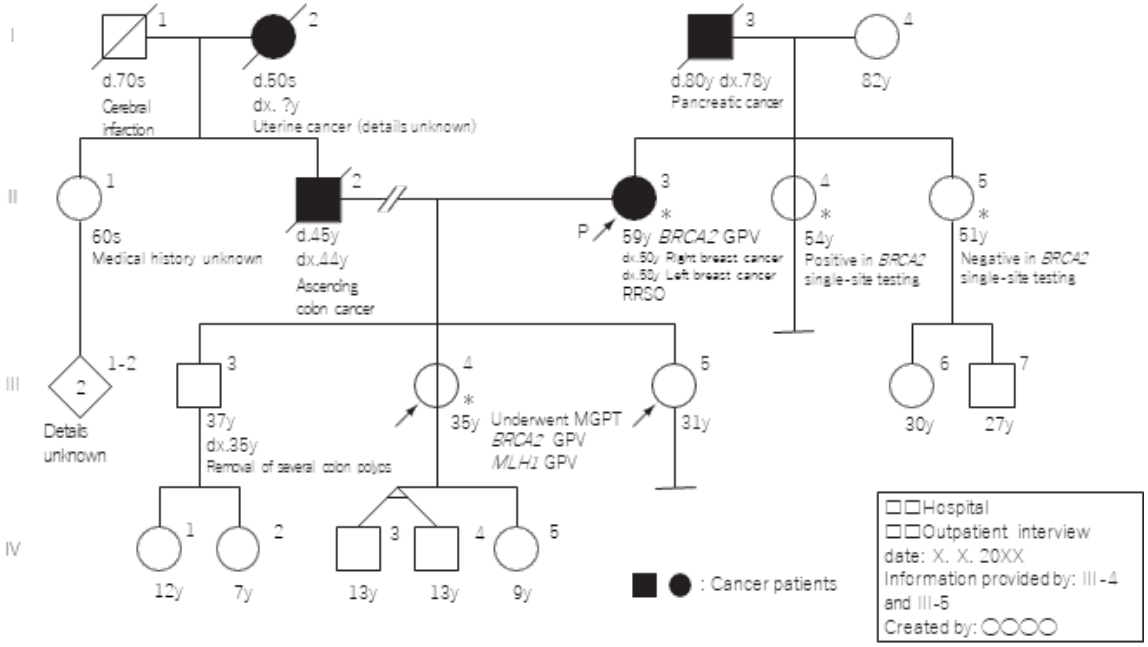


Figure 5-3. Definition of relationship lines

Adapted from "Textbook for Hereditary Tumor Specialists" [6)]

Figure 5-4. Example of genealogical tree



GPV: germline pathogenic variant
RRSO: risk-reducing salpingo-oophorectomy

■ References

1) Schneider KA, Chittenden A, Shannon KM. Counseling about cancer: strategies for genetic counseling, 4th edition. Wiley Blackwell, 2023.
2) Bennett RL, Steinhaus KA, Uhrich SB, et al. Recommendations for standardized human pedigree nomenclature. Pedigree Standardization Task Force of the National Society of Genetic Counselors. Am J Hum Genet. 1995;56(3):745-52. [PMID: 7887430]
3) Bennett RL, French KS, Resta RG, et al. Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Couns. 2008;17(5):424-33. [PMID: 18792771]
4) Bennett RL, French KS, Resta RG, et al. Practice resource-focused revision: Standardized pedigree nomenclature update centered on sex and gender inclusivity: A practice resource of the National Society of Genetic Counselors. J Genet Couns. 2022;31(6):1238-48. [PMID: 36106433].
5) Terminology Committee of the Japanese Society for Genetic Counseling. Practical Resource [Focused Revision] Updating the Standard Genealogy Terminology System with a Focus on Sex and Gender Inclusivity: Practical Resource of the U.S. National Society of Genetic Counselors. Japanese Journal of Genetic Counseling. 2023;44(3):83-95.
6) Japanese Society for Hereditary Tumors, supervised. Textbook Preparation Committee of the Japanese Society for Hereditary Tumors, ed. Textbook for Hereditary Tumor Specialists. Herusu Publishing Co., Inc. 2022.

2. Description of genomic variants

Genomic changes are commonly described using the method set by the Human Genome Variation Society (HGVS) (https://hgvs-nomenclature.org).

1. Genome reference sequences

While the specific reference sequence is typically not included, the so-called 'genome build' is listed; a genome build is an attempt to reconstruct the entire base sequence of the human genome based on all data available at the time of the construction of the reference sequence. Genome builds are denoted in two ways: "hg" followed by a number (e.g., hg18, hg19, and hg38) or "GRCh/NCBI" followed by a number (e.g., NCBI35, NCBI36, GRCh37, and GRCh38). The most frequently used genome builds are "hg18/NCBI36" (since March 2006), "hg19/GRCh37" (since February 2009), and "hg38/GRCh38" (since December 2013).

2. Symbols used in reference sequences

Variants described at the DNA level are generally denoted in relation to a specific gene based on a so-called "coding DNA reference sequence." The standard description of variants takes the format of "prefix. position(s)_change." If a coding DNA reference sequence is used, the prefix "c." is used to describe the variant (e.g., c.4375C>T). Since reliable reference sequences of the entire human genome are now available, it is also becoming common to describe variants based on a genomic reference sequence using the prefix "g." (e.g., g.32407761G>A). Additionally, descriptive methods for the RNA level (prefix "r.") and/or protein level (prefix "p.") may be used.

***Side note 5-2**

A coding DNA reference sequence is a DNA sequence serving as a template for mRNA that is translated into a protein, bounded by the start and stop codons of the mRNA, and it is the most frequently used reference sequence in human diagnosis (descriptions start with the prefix "c": e.g., NM_004006.3: c.4375C>T). Variant descriptions based on this format can be easily used, as they are directly linked to the encoded protein.

3. Variant location

(1) Changes at the genomic DNA level are denoted by the prefix "g." To number genomic positions, the beginning of the reference genome sequence is counted as 1.

(2) Changes at the coding DNA level are denoted by the prefix "c.," and the "A" of the start codon "ATG" (translation start point) is counted as 1. Coding DNA is a DNA sequence that is translated into

protein, and it does not contain introns. Thus, the position of an intron is denoted by using a '+' or '-' sign to indicate the position from the adjacent exon.

(3) Descriptions at the RNA level are denoted by the prefix "r.," and the description method for the DNA level is used. However, RNA base sequences are written in lowercase letters, and 'T' in DNA is expressed as 'u' in RNA. In addition, "r." is used for splicing abnormalities, for example.

(4) Descriptions at the protein level are denoted by the prefix "p.," and the methionine at the start of translation is counted as 1. Amino acids can be denoted with either three letters or one letter (Tables 5-1 and 5-2). A description is made using the position number of the codon changed due to the variant.

To express the position of an intron, the position number from the adjacent exon is indicated using a '+' or '-' sign. The position before the protein translation start site is indicated by a '-' sign (e.g., "c.-26"), and the position after the protein translation stop site is indicated by an asterisk (e.g., "c. *85"). Intron sequences are numbered in the form of 'c.530+6' or 'c.531-23.'

Table 5-1. Amino acid notations

One-letter notation	Full notation	Three-letter notation	One-letter notation	Full notation	Three-letter notation
A	Alanine	Ala	H	Histidine	His
F	Phenylalanine	Phe	M	Methionine	Met
K	Lysine	Lys	R	Arginine	Arg
P	Proline	Pro	W	Tryptophan	Trp
T	Threonine	Thr	E	Glutamic acid	Glu
C	Cysteine	Cys	I	Isoleucine	Ile
G	Glycine	Gly	N	Asparagine	Asn
L	Leucine	Leu	S	Serine	Ser
Q	Glutamine	Gln	Y	Tyrosine	Tyr
V	Valine	Val	*	Stop codon	Ter
D	Aspartic acid	Asp			

Table 5-2. Codon table

1st base	2nd base				3rd base
	U	C	A	G	
U	UUU Phe	UCU Ser	UAU Tyr	UGU Cys	U

	UUC Phe	UCC Ser	UAC Tyr	UGC Cys	C
	UUA Leu	UCA Ser	UAA ＊/Ter	UGA ＊/Ter	A
	UUG Leu	UCG Ser	UAG ＊/Ter	UGG Trp	G
C	CUU Leu	CCU Pro	CAU His	CGU Arg	U
	CUC Leu	CCC Pro	CAC His	CGC Arg	C
	CUA Leu	CCA Pro	CAA Gln	CGA Arg	A
	CUG Leu	CCG Pro	CAG Gln	CGG Arg	G
A	AUU Ile	ACU Thr	AAU Asn	AGU Ser	U
	AUC Ile	ACC Thr	AAC Asn	AGC Ser	C
	AUA Ile	ACA Thr	AAA Lys	AGA Arg	A
	AUG Met	ACG Thr	AAG Lys	AGG Arg	G
G	GUU Val	GCU Ala	GAU Asp	GGU Gly	U
	GUC Val	GCC Ala	GAC Asp	GGC Gly	C
	GUA Val	GCA Ala	GAA Glu	GGA Gly	A
	GUG Val	GCG Ala	GAG Glu	GGG Gly	G

4. Types and notations of variants

Examples of variants denoted using the standard method are shown below:

● Substitution: Substitution refers to the replacement of one base in the DNA code by another. Substitution at the DNA or RNA level is indicated by ">."

▶ c.4375C>T: The C nucleotide at position c.4375 has been changed to T.

● Deletion: Deletion refers to the absence of one or more bases in the DNA code. A deletion is indicated by "del."

▶ c.4375_4379del: The nucleotides from position c.4375 to c.4379 (CGATT) are absent (deleted). It may also be denoted as 'c.4375_4379delCGATT.'

● Duplication: Duplication refers to the repetition of one or more bases of the DNA code. Duplication is indicated by "dup."

▶ c.4375_4385dup: Two sets of nucleotides from position c.4375 to c.4385 (CGATTATTCCA) are present (duplication). It may also be denoted as 'c.4375_4385dupCGATTATTCCA' or 'c.4385_4386insCGATTATTCCA.' Although these are not the correct notations set by the HGVS, they are used to accurately describe the duplicated region.

● Insertion: Insertion refers to the introduction of one or more bases in the DNA code. Insertion is indicated by "ins."

▶ c.4375_4376insACCT: A new sequence "ACCT" has been inserted between positions c.4375 and c.4376.

● Deletion/insertion (delins): One or more bases in the DNA code are deleted and replaced by several new bases. Deletion/insertion is indicated by “delins.”

▶ c.4375_4376delinsAGTT: The nucleotides from position c.4375 to c.4376 (CG) have been deleted and replaced by a new sequence “AGTT.” It may also be denoted as ‘c.4375_4376delCGinsAGTT.’

There are many other variant types, although they occur less frequently.

■ References

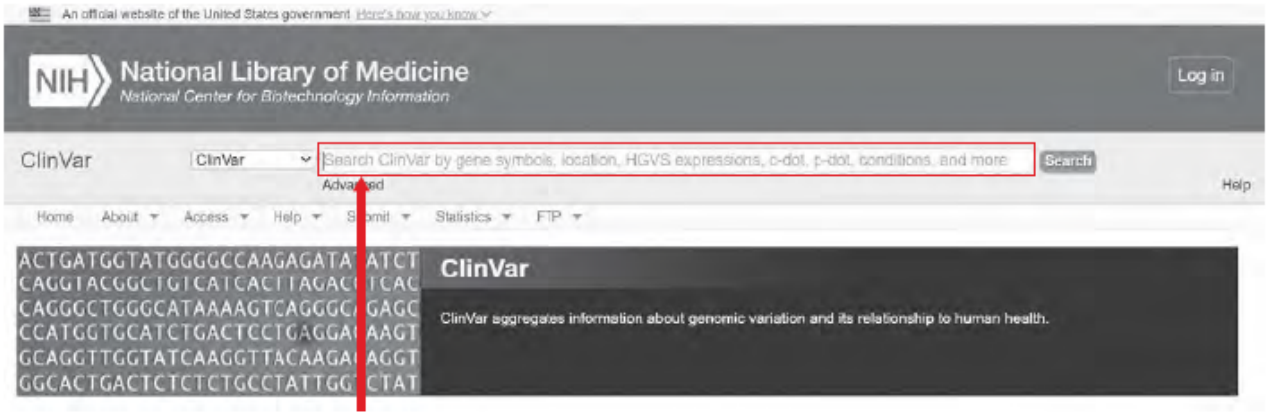
1) Japanese Society for Cancer of the Colon and Rectum. Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition. Kanehara Publishing Co., Ltd.
2) Human Genome Variation Society (HGVS)
https://hgvs-nomenclature.org

3. How to use ClinVar

For medical purposes, the National Center for Biotechnology Information (NCBI), a division of the National Library of Medicine (NLM) under the U.S. National Institutes of Health (NIH), collects and publicly shares data on disease-associated genetic variants without restriction. This open-access database, known as ClinVar, includes information such as gene names, variant locations, clinical significance, and disease associations. ClinVar is also commonly used in the interpretation of genetic testing results. For the evaluation of variants, the 2015 ACMG/AMP guidelines do not recommend the direct use of the pathogenicity interpretation of variants included in databases (PP5/BP6). However, given various issues and limitations, different databases and tools (**Table 5-3**) are used for the evaluation of variants in some cases. Among those, the use of ClinVar, also discussed in BQ5, is introduced below.

[Access URL]

https://www.ncbi.nlm.nih.gov/clinvar/

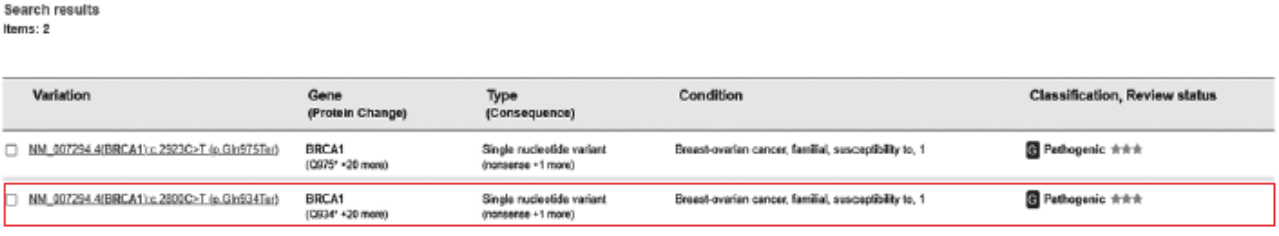


(1) Enter the gene name and variant you wish to search (red arrow).

Example: BRCA1 c.2800C T>

(2) Review the search result.

Confirm that "NM_007294.4 (BRCA1): c.2800C>T (p.Gln934Ter)" is listed.



For this variant, the item “Classification, Review status” is found on the right side, denoted with “Pathogenic★★★.”

“Classification” indicates a variant classification based on the 2015 ACMG/AMP guidelines.

“Review status” indicates the confidence level of the clinical importance provided by the registrant.

★★★★ : Approved as a clinical practice guideline by the ClinGen Steering Committee

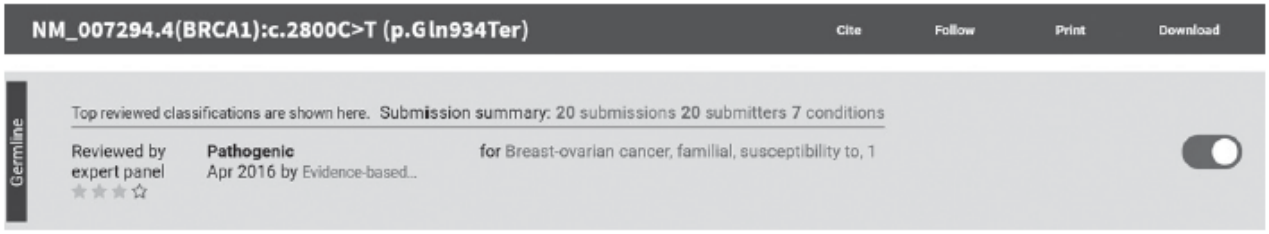
★★★ : Reviewed and approved by the expert panel

★★ : Consistent clinical importance has been presented by multiple registrants

★ : The criteria used to determine clinical significance (text describing the criteria) were registered by one registrant

None

(3) Click on the relevant item (Variation) to move to the page for a detailed explanation.



Further information is provided in the following sections:

Variant Details	Details of the variant, such as variant notation for each reference sequence, ClinVar ID, and a link to dbSNP
Genes	Details of genes, such as a link to OMIM
Conditions - Germline	Details of diseases registered in ClinVar, etc.
Submissions - Germline	Details of registrants registered in ClinVar, details of the basis for their decision, etc.
Germline Functional Evidence	Evidence from functional analysis adopted by ClinVar
Citations for germline classification of this variant	Reference literature

Table 5-3. Databases and tools used as a reference for variant evaluation, etc.

Name	URL
Public databases of variants	
ClinGen	https://clinicalgenome.org/
dbSNP	https://www.ncbi.nlm.nih.gov/snp/

ClinVar	https://www.ncbi.nlm.nih.gov/clinvar/
MGeND	https://mgend.ncgm.go.jp/
Databases of variant allele frequency in the general population	
gnomAD	https://gnomad.broadinstitute.org/
jMorp	https://jmorp.megabank.tohoku.ac.jp/
HGVD	https://www.hgvd.genome.med.kyoto-u.ac.jp/
Tools for confirming positions and notations of nucleotide sequences	
MANE Collaboration	https://tark.ensembl.org/web/mane_project/
Sequence Variant Nomenclature	http://varnomen.hgvs.org/
Mutalyzer 3	https://v3.mutalyzer.nl/
Lift over variants	https://liftover.broadinstitute.org/
GGGenome	https://gggenome.dbcls.jp/ja/
GGRNA	https://ggrna.dbcls.jp/ja/
Tools for predicting splicing abnormalities	
varSEAK	https://varseak.bio/index.php
SpliceAI	https://spliceailookup.broadinstitute.org/#
Human Splicing Finder	http://umd.be/Redirect.html
NNSPLICE 0.9 version	https://www.fruitfly.org/seq_tools/splice.html
MaxEntScan	http://hollywood.mit.edu/burgelab/maxent/Xmaxentscan_scoreseq.html
GeneSplicer	https://www.cbcb.umd.edu/software/GeneSplicer/gene_spl.shtml
TraP	https://trap-score.org/index.jsp
Databases and tools used for gene-specific evaluations	
ENIGMA	https://enigmaconsortium.org/
InSiGHT variant classifications	http://insight-database.org/
The *TP53* database	https://tp53.isb-cgc.org/
Cleveland Clinic risk assessment tool	https://www.lerner.ccf.org/genomic-medicine/ccscore/
COOL（Cosegregation OnLine）v2	http://bjfenglab.org/cool2/index.html
COOL v3（beta varsion）	https://fenglab.chpc.utah.edu/cool3/manual.html
In silico prediction tools	
PRIORS	https://hci-priors.hci.utah.edu/PRIORS/

Align-GVGD	http://agvgd.hci.utah.edu/about.php
PolyPhen-2 (Polymorphism Phenotyping v2)	http://genetics.bwh.harvard.edu/pph2/index.shtml
SIFT	https://sift.bii.a-star.edu.sg/
REVEL	https://sites.google.com/site/revelgenomics/
mutation t@sting	https://www.genecascade.org/MutationTaster2021/#transcript
BLOSUM62	https://ftp.ncbi.nlm.nih.gov/blast/matrices/
Databases for the comprehensive search/evaluation of variant information	
Varsome	https://varsome.com/
Franklin	https://franklin.genoox.com/clinical-db/home
Mastermind	https://mastermind.genomenon.com/
Mutation@A Glance	https://mutation.nagahama-i-bio.ac.jp/
Variant Effect Predictor	https://asia.ensembl.org/Tools/VEP
dbNSFP	http://database.liulab.science/dbNSFP
Databases of somatic mutations	
OncoKB	https://www.oncokb.org/
COSMIC	https://cancer.sanger.ac.uk/cosmic
cBioPortal	https://www.cbioportal.org/

4. Professional Qualifications and Systems Involved in the treatment of hereditary tumor syndromes (as of July 2024)

1. Hereditary tumor specialist

[URL]

https://jsht-info.jp/medical_personnel/specialist/familiar_tumors/

[Accredited societies and organizations]

The Japanese Society for Hereditary Tumors

[Targets]

Physicians

[Application eligibility]

(1) A person who holds a medical license in Japan

(2) A specialist physician (certified physician) of a basic specialty society recognized by the Specialist System Subcommittee

(3) A person who has been a member of the Japanese Society for Hereditary Tumors for at least three consecutive years

(4) A person who has completed at least three years of training at a training facility in accordance with the training curriculum

(5) A person who has made achievements related to hereditary tumors in the five years prior to the time of application

[Roles]

Hereditary tumor specialists promote appropriate medical care related to hereditary tumors with a thorough knowledge of oncology and genetics. They also contribute to the welfare of the public by disseminating knowledge about hereditary tumors to enhance medical practices and services in this field.

2. Clinical genetics specialist

[URL]

https://www.jbmg.jp/

[Accredited societies and organizations]

Japanese Board of Medical Genetics and Genomics, Clinical Genetics (Japan Society of Human Genetics and Japanese Society for Genetic Counseling)

[Targets]

Physicians

[Application eligibility]

(1) A person who has been a member of the Japan Society of Human Genetics or the Japanese Society for Genetic Counseling for at least three consecutive years

(2) A person who has been working as a specialist physician of a basic specialty society set by the Japanese Medical Specialty Board or a specialist physician (certified physician) recognized by the Japanese Board

of Medical Genetics and Genomics, Clinical Genetics for at least three consecutive years
(3) A person who has completed at least three years of training in clinical genetics and practiced genetic medicine, including genetic counseling, with the guidance of a supervising responsible physician affiliated with an accredited training facility or a supervising physician affiliated with a non-accredited training facility
(4) A person who is engaged in academic activities related to genetic medicine (such as manuscript publications and conference presentations)
(5) A person who possesses the competencies described in the Behavioral Objectives of Clinical Genetics Specialists

[Roles]

Clinical genetics specialists strive to deliver high-quality clinical genetic care and to contribute to the advancement of the field of clinical genetics. Their goal is to provide appropriate and individualized genetic medicine to patients and their families; while also helping to build a society in which all individuals can utilize genomic information in a healthy and informed manner, guided by their own decision-making.

3. Certified genetic counselor

[URL]

https://plaza.umin.ac.jp/~GC/

[Accredited societies and organizations]

Certified Genetic Counselor System Committee

[Targets]

Those who have completed a certification training program for genetic counselors

[Application eligibility]

Those who have completed a certification training program for genetic counselors at a graduate school are eligible to take the certification examination for genetic counselors. In addition, the applicant must be a member of the Japanese Society for Genetic Counseling or the Japan Society of Human Genetics for at least two consecutive years at the time of application.

[Roles]

Certified genetic counselors provide accurate genetic information and related resources, including details on available social support systems, to patients and families in need of genetic medical care. They also assist individuals in making informed and autonomous decisions by offering psychological and social support throughout the process.

4. Nurse specialist in genetics nursing

[URL]

https://www.nurse.or.jp/nursing/qualification/vision/cns/index.html

[Accredited societies and organizations]

Japanese Nursing Association

[Targets]

Nurses

[Application eligibility]

(1) Licensing requirement: The applicant must hold a nursing license in Japan.
(2) Educational requirement: The applicant must have completed a master's degree program at a

graduate school of nursing or related fields.

(3) Practical training requirement: The applicant must have the necessary practical training as a nurse specialist. The applicant must have completed a total of at least five years of practical training after obtaining a nursing qualification. Of those, a total of at least three years must have been in the field of genetics nursing.

[Roles]

Nurse specialists in genetics nursing assess the unique genetic issues faced by each individual and provide decision-making support related to diagnosis, prevention, and treatment. They offer lifelong care to help improve QOL and aim to establish a system that enables patients to access appropriate medical care across generations. Additionally, they contribute to the advancement of genomic medicine through their specialized practice.

5. Hereditary tumor coordinator

[URL]

https://jsht-info.jp/medical_personnel/specialist/fcc/coordinator.html

[Accredited societies and organizations]

The Japanese Society for Hereditary Tumors

[Targets]

Physicians, nurses, midwives, public health nurses, pharmacists, clinical laboratory technicians, etc.

[Application eligibility]

(1) A person who has been a member of the Japanese Society for Hereditary Tumors for at least three years at the time of application

(2) A person who has attended at least three seminars on genetic tumors held by the Japanese Society for Hereditary Tumors by the time of application

(3) The applicant must have a medical qualification (physician, nurse, midwife, public health nurse, pharmacist, clinical laboratory technician, etc.). Also, the applicant must have worked at a medical institution involved in cancer care for at least two years at the time of application and have practical experience in at least five cases of hereditary tumors (some of them may be genomic cancer treatment).

[Roles]

With comprehensive expertise in oncology and cancer genetics, hereditary tumor coordinators support patients and their families in accessing appropriate care for hereditary tumors and cancer genome medicine. They also contribute to public well-being by promoting awareness of hereditary tumors and working to enhance medical practices in this field.

6. Genetic expert

[URL]

http://www.gene-dt.jp/GE.html

[Accredited societies and organizations]

Japanese Society for Gene Diagnosis and Therapy

[Targets]

Those who are involved in somatic genetic testing and genetic testing and contribute to medical care, regardless of their occupation

[Application eligibility]

(1) A member of the Japanese Society for Gene Diagnosis and Therapy

(2) A person who has earned at least 30 credits for academic activities (such as manuscript publications, conference presentations, and participation in workshops and seminars) related to genetic medicine, genetic testing, somatic genetic testing, and other human gene-related testing in the past five years

(3) A person who has attended at least two sessions of the Clinical Genetic Information Search Seminar (including the former Genetic Technology Seminar) held by the Japanese Society for Gene Diagnosis and Therapy and the Genetic Expert Certification System Committee in the past five years

(4) A person who has at least three years of work experience in a facility involved in genetic medicine, genetic testing, somatic genetic testing, and other human gene-related testing for medical purposes, which must be attested by two individuals who can provide recommendations. The facilities include universities, companies, research institutes, hospitals, educational institutions, clinical testing centers, and government offices.

(5) One of the above recommenders must be a person in charge or a leader of genetic medicine, genetic testing, somatic gene testing, or other human gene-related testing at the facility. The other recommender must be an officer or council member of the Japanese Society for Gene Diagnosis and Therapy.

(6) The above recommendations are not required for applicants who hold the qualification of clinical genetics specialist, certified clinical cytogeneticist, or certified genetic counselor.

(7) For the number of years required to qualify for the certification examination, please refer to the website of the Japanese Society for Gene Diagnosis and Therapy (http://www.gene-dt.jp/pdf_GE/gene_GE_examplan2023.pdf).

[Roles]

In conducting genetic testing, including somatic and other human gene-related tests, and handling genetic information, genetic experts are responsible for appropriately selecting relevant data, accurately interpreting test and analysis results, and promptly reporting and clearly explaining their significance to medical professionals. They also play a key role in ensuring the accuracy and quality control of testing and analysis processes, and in advancing the development of testing methodologies through the use of databases and other scientific resources.

5. Explanatory and consent documents (model documents) for multigene panel testing (MGPT) for the diagnosis of hereditary cancer syndrome

For medical institutions considering the introduction of MGPT, the “Explanatory and Consent Documents (Model Documents) for MGPT in the Diagnosis of Hereditary Cancer Syndrome” have been prepared by the group on MHLW Research on Promotion of Cancer Control Program Grant Number JPMH 23EA1037.

These model documents should be used at the discretion and responsibility of each medical institution, after reviewing and making any necessary modifications. It is important to note that the contents are based on general MGPT practices and may not be directly applicable to all institutions. Within the documents, sections that require additions or modifications depending on each facility’s specific circumstances are highlighted.

The model documents can be downloaded from the website (https://www.iden-gan.jp) of MHLW Research on Promotion of Cancer Control Program Grant Number JPMH 23EA1037. As they are scheduled to be revised periodically, please refer to the website for the latest version.

[Website URL and QR code]
https://www.iden-gan.jp

6. Guidelines for cancer susceptibility genes and hereditary tumor syndromes

Gene	Syndrome	Guidelines					Variant evaluation criteria***
		Japan*	NCCN Breast, Ovarian, and Pancreatic 2024 ver. 3**	NCCN Colorectal, Endometrial, and Gastric 2024 ver. 1**	Other international guidelines, etc. discussed in Chapter 4**	ACMG SF ver. 3.2**	Gene-specific criteria
APC	FAMILIAL ADENOMATOUS POLYPOSIS 1; FAP1 (OMIM 175100) (GRJ APC-related polyposis)	Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition	○	◎		△	○
ATM	BREAST CANCER {Breast cancer, susceptibility to} (OMIM 114480)	None	◎	○			○
AXIN2	OLIGODONTIA-COLORECTAL CANCER SYNDROME; ODCRCS (OMIM 608615)	None		◎			
BAP1	TUMOR PREDISPOSITION SYNDROME 1; TPDS1 (OMIM 614327) (GRJ *BAP1* tumor predisposition syndrome)	None	○		◎		
BARD1	BREAST CANCER {Breast cancer, susceptibility to} (OMIM 114480)	None	◎				
BLM	—	None	○	◎			
BMPR1A	JUVENILE POLYPOSIS SYNDROME; JPS (OMIM 174900) (GRJ juvenile polyposis syndrome)	Clinical Practice Guidelines for Juvenile Polyposis Syndrome in	○	◎	◎	△	

		Children and Adults (2020 Edition)					
BRCA1	BREAST-OVARIAN CANCER, FAMILIAL, SUSCEPTIBILITY TO, 1; BROVCA1 (OMIM 604370) (GRJ BRCA1- and BRCA2-related hereditary breast and ovarian cancer)	Clinical Practice Guidelines for Hereditary Breast and Ovarian Cancer (HBOC), 2024 Edition (2024), 2nd Edition	◎	○		△	○
BRCA2	BREAST-OVARIAN CANCER, FAMILIAL, SUSCEPTIBILITY TO, 2; BROVCA2 (OMIM 612555) (GRJ BRCA1- and BRCA2-related hereditary breast and ovarian cancer)	Clinical Practice Guidelines for Hereditary Breast and Ovarian Cancer (HBOC), 2024 Edition (2024), 2nd Edition	◎	○		△	○
BRIP1	BREAST CANCER {Breast cancer, early-onset, susceptibility to} (OMIM 114480)	None	◎				
CDH1	DIFFUSE GASTRIC AND LOBULAR BREAST CANCER SYNDROME; DGLBC (OMIM 137215) (GRJ hereditary diffuse gastric cancer)	None	◎	◎	◎		○
CDK4	MELANOMA, CUTANEOUS MALIGNANT, SUSCEPTIBILITY TO, 3; CMM3 (OMIM 609048)	None	○				
CDKN2A	MELANOMA-PANCREATIC CANCER SYNDROME (OMIM 606719)	None	◎		◎		
CHEK2	TUMOR PREDISPOSITION SYNDROME 4; TPDS4 (OMIM 609265)	None	◎	◎	◎		
DICER1	GOITER, MULTINODULAR 1, WITH OR WITHOUT SERTOLI-LEYDIG CELL TUMORS; MNG (OMIM 138800) and/or PLEUROPULMONARY BLASTOMA; PPB (OMIM 601200) (GRJ DICER1 tumor predisposition)	None	○		◎		○
EPCAM	LYNCH SYNDROME 8; LYNCH8 (OMIM 613244) (GRJ Lynch syndrome)	Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition	◎	◎			
FH	HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER; HLRCC (OMIM 150800) (GRJ FH tumor predisposition syndrome)	None	○		◎		

FLCN	BIRT-HOGG-DUBE SYNDROME 1; BHD1 (OMIM 135150) (GRJ Birt-Hogg-Dubé syndrome)	None	○		◎		
GALNT12	COLORECTAL CANCER, SUSCEPTIBILITY TO, 1; CRCS1 (OMIM 608812)	None		◎			
GREM1	POLYPOSIS SYNDROME, HEREDITARY MIXED, 1; HMPS1 (OMIM 601228)	None		◎			
HOXB13	PROSTATE CANCER, HEREDITARY, 9; HPC9 (OMIM 610997)	None	○		◎		
MAX	PHEOCHROMOCYTOMA, SUSCEPTIBILITY TO (OMIM 171300) (GRJ hereditary paraganglioma and pheochromocytoma syndrome)	Clinical Practice Guidelines for Pheochromocytoma and Paraganglioma, 2018 Edition	○		◎	△	
MEN1	MULTIPLE ENDOCRINE NEOPLASIA, TYPE I; MEN1 (OMIM 131100) (GRJ multiple endocrine neoplasia type 1)	Guidebook for Management of Multiple Endocrine Neoplasia, Clinical Practice Guidelines for Pancreatic and Gastrointestinal Neuroendocrine Neoplasia (NEN), 2019 Edition (2nd Edition)	○		◎	△	
MET	RENAL CELL CARCINOMA, PAPILLARY, 1; RCCP1 (OMIM 605074)	None			◎		
MLH1	LYNCH SYNDROME 2; LYNCH2 (OMIM 609310) (GRJ Lynch syndrome)	Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition	◎	◎	◎	△	
MSH2	LYNCH SYNDROME 1; LYNCH1 (OMIM 120435) (GRJ Lynch syndrome)	Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition	◎	◎	◎	△	
MSH3	FAMILIAL ADENOMATOUS POLYPOSIS 4; FAP4 (OMIM 617100)	Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition		◎			
MSH6	LYNCH SYNDROME 5; LYNCH5 (OMIM 614350) (GRJ Lynch syndrome)	Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition	◎	◎	◎	△	

MUTYH	FAMILIAL ADENOMATOUS POLYPOSIS 2; FAP2 (OMIM 608456) (GRJ MUTYH polyposis)	Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition	○	◎	◎	△	
NF1	NEUROFIBROMATOSIS, TYPE I; NF1 (OMIM 162200) (GRJ neurofibromatosis type 1)	Clinical Practice Guidelines for Neurofibromatosis Type 1 (von Recklinghausen disease), 2018 Edition. Japan Society for Neuro-Oncology (ed.): Clinical Practice Guidelines for Brain Tumor, 2021 Edition. Guidelines for Optic Pathway/Hypothalamic Glioma (OPHG), 1st Edition. Committee for the Creation of Clinical Practice Guidelines for Plexiform Neurofibroma/Malignant Peripheral Nerve Sheath Tumor (ed.): Clinical Practice Guidelines for Plexiform Neurofibroma/Malignant Peripheral Nerve Sheath Tumor	◎		◎		
NF2	SCHWANNOMATOSIS, VESTIBULAR; SWNV (OMIM 101000) (GRJ neurofibromatosis type 2)	Treatment Guidelines for Neurofibromatosis Type 2 (NF2) (Revised October 2016)			◎	△	
NTHL1	FAMILIAL ADENOMATOUS POLYPOSIS 3; FAP3 (OMIM 616415) (GRJ NTHL1 tumor syndrome)	None	○	◎	◎		
PALB2	BREAST-OVARIAN CANCER, FAMILIAL, SUSCEPTIBILITY TO, 5; BROVCA5 (OMIM 620442)	None	◎			△	○
PMS2	LYNCH SYNDROME 4; LYNCH4 (OMIM 614337) (GRJ Lynch syndrome)	Clinical Practice Guidelines for Hereditary Colorectal Cancer, 2024 Edition	◎	◎	◎	△	
POLD1	COLORECTAL CANCER, SUSCEPTIBILITY TO, 10; CRCS10 (OMIM 612591)	None		◎			
POLE	COLORECTAL CANCER, SUSCEPTIBILITY TO, 12; CRCS12	None		◎			

	(OMIM 615083)						
PTEN	COWDEN SYNDROME 1; CWS1 (OMIM 158350) (GRJ PTEN hamartoma tumor syndrome)	Clinical Practice Guidelines for Cowden Syndrome/*PTEN* Hamartoma Tumor Syndrome in Children and Adults (2020 Edition)	◎	◎		△	○
RAD51C	BREAST-OVARIAN CANCER, FAMILIAL, SUSCEPTIBILITY TO, 3; BROVCA3 (OMIM 613399)	None	◎				○
RAD51D	BREAST-OVARIAN CANCER, FAMILIAL, SUSCEPTIBILITY TO, 4; BROVCA4 (OMIM 614291)	None	◎				
RB1	RETINOBLASTOMA; RB1 (OMIM 180200) (GRJ retinoblastoma)	Clinical Practice Guidelines for Pediatric Cancer, 2016 Edition, 2nd Edition			◎	△	
RET	MULTIPLE ENDOCRINE NEOPLASIA, TYPE ⅡA; MEN2A (OMIM 171400) and MULTIPLE ENDOCRINE NEOPLASIA, TYPE ⅡB; MEN2B (OMIM 162300) (GRJ multiple endocrine neoplasia type 2)	Guidebook for Management of Multiple Endocrine Neoplasia	○		◎	△	
RNF43	SESSILE SERRATED POLYPOSIS CANCER SYNDROME; SSPCS (OMIM 617108)	None		◎			
RPS20	—	None		◎			
SDHA	PHEOCHROMOCYTOMA/PARAGANGLIOMA SYNDROME 5; PPGL5 (OMIM 614165) (GRJ hereditary paraganglioma and pheochromocytoma syndrome)	Clinical Practice Guidelines for Pheochromocytoma and Paraganglioma, 2018 Edition	○		◎		
SDHAF2	PHEOCHROMOCYTOMA/PARAGANGLIOMA SYNDROME 2; PPGL2 (OMIM 601650) (GRJ hereditary paraganglioma and pheochromocytoma syndrome)	Clinical Practice Guidelines for Pheochromocytoma and Paraganglioma, 2018 Edition	○		◎	△	

SDHB	PHEOCHROMOCYTOMA/PARAGANGLIOMA SYNDROME 4; PPGL4 (OMIM 115310) (GRJ hereditary paraganglioma and pheochromocytoma syndrome)	Clinical Practice Guidelines for Pheochromocytoma and Paraganglioma, 2018 Edition	○		◎	△	
SDHC	PHEOCHROMOCYTOMA/PARAGANGLIOMA SYNDROME 3; PPGL3 (OMIM 605373) (GRJ hereditary paraganglioma and pheochromocytoma syndrome)	Clinical Practice Guidelines for Pheochromocytoma and Paraganglioma, 2018 Edition	○		◎	△	
SDHD	PHEOCHROMOCYTOMA/PARAGANGLIOMA SYNDROME 1; PPGL1 (OMIM 168000) (GRJ hereditary paraganglioma and pheochromocytoma syndrome)	Clinical Practice Guidelines for Pheochromocytoma and Paraganglioma, 2018 Edition	○		◎	△	
SMAD4	JUVENILE POLYPOSIS SYNDROME; JPS (OMIM 174900) (GRJ juvenile polyposis syndrome)	Clinical Practice Guidelines for Juvenile Polyposis Syndrome in Children and Adults (2020 Edition)	○	◎	◎	△	
STK11	PEUTZ-JEGHERS SYNDROME; PJS (OMIM 175200) (GRJ Peutz-Jeghers syndrome)	Clinical Practice Guidelines for Peutz-Jeghers Syndrome in Children and Adults (2020 Edition)	◎	◎	◎	△	
TMEM127	PHEOCHROMOCYTOMA, SUSCEPTIBILITY TO (OMIM 171300) (GRJ hereditary paraganglioma and pheochromocytoma syndrome)	Clinical Practice Guidelines for Pheochromocytoma and Paraganglioma, 2018 Edition	○		◎	△	
TP53	LI-FRAUMENI SYNDROME; LFS (OMIM 151623) (GRJ Li-Fraumeni syndrome)	Clinical Practice Guidelines for Li-Fraumeni Syndrome, 2019 Edition	◎	◎	◎	△	○
TSC1	TUBEROUS SCLEROSIS 1; TSC1 (OMIM 191100) (GRJ tuberous sclerosis)	Committee for the Revision of "Diagnostic Criteria and Treatment Guidelines for Tuberous Sclerosis" (ed.): Diagnostic Criteria and Treatment Guidelines for Tuberous Sclerosis (Revised Edition). Japan Society	○		◎	△	

		for Neuro-Oncology (ed.): Clinical Practice Guidelines for Brain Tumor. Pediatric Brain Tumor "Subependymal Giant Cell Astrocytoma (SEGA)" Japanese Urological Association and Japanese Society of Tuberous Sclerosis Complex (ed.): Clinical Practice Guidelines for Renal Angiomyolipoma Associated with Tuberous Sclerosis (2016 Edition)					
TSC2	TUBEROUS SCLEROSIS 2; TSC2 (OMIM 613254) (GRJ tuberous sclerosis)	Committee for the Revision of "Diagnostic Criteria and Treatment Guidelines for Tuberous Sclerosis" (ed.): Diagnostic Criteria and Treatment Guidelines for Tuberous Sclerosis (Revised Edition). Japan Society for Neuro-Oncology (ed.): Clinical Practice Guidelines for Brain Tumor. Pediatric Brain Tumor "Subependymal Giant Cell Astrocytoma (SEGA)" Japanese Urological Association and Japanese Society of Tuberous Sclerosis Complex (ed.): Clinical Practice Guidelines for Renal Angiomyolipoma Associated with Tuberous Sclerosis (2017 Edition)	○		◎		
VHL	VON HIPPEL-LINDAU SYNDROME; VHLS (OMIM 193300) (GRJ von Hippel-Lindau disease)	Clinical Practice Guidelines for von Hippel-Lindau Disease, 2017 Edition. Group for "Research on the Actual Status and Standardization of Medical Treatment of Hereditary Diseases Causing Various Endocrine Abnormalities (Multiple	○		◎	△	○

		Endocrine Neoplasia and von Hippel-Lindau Disease)." Clinical Practice Guide for VHL Disease (2024). Group for "Comprehensive Research on von Hippel-Lindau Disease for the Investigation of the Actual Condition, Establishment of Medical Treatment System, and Improvement of QOL"					
WT1	WILMS TUMOR 1; WT1 (OMIM 194070) (GRJ Wilms tumor predisposition)	None	○			△	

*: Only domestic guidelines with clear surveillance methods are shown.

**: Those with a description of surveillance methods in the NCCN guidelines are indicated with ◎, and those without a clear description of surveillance methods are indicated with ○. Also, those with no description of surveillance methods are indicated with a blank cell. In addition, those that are specified as disclosure-target genes of secondary findings in ACMG SF ver. 3.2 are indicated with △.

***: Those for which gene-specific criteria have been published in ClinGen's Criteria Specification Registry are indicated with ○.

Conclusion

I would like to express my sincere gratitude to all the authors, collaborators, external evaluators, Ms. Akane Nakagawa of Kanehara Publishing Co., Ltd., and many others, including the committee members related to the Japanese Society for Hereditary Tumors, for their efforts in editing "Guidance for hereditary cancer syndrome with Multigene Panel Testing (MGPT)".

Although the introduction of MGPT has only been recent, its need in daily medical practice is rapidly expanding. This is attributed to the growing recognition of the importance of genetic diagnosis and the usefulness of appropriate management based on genetic diagnosis, which are now widely recognized among medical professionals, as well as among patients, their families, and the general public.

The expansion of MGPT-medical practice may identify additional hereditary cancer syndromes that need to be examined and increase the workload for variant evaluation. This raises concerns that differences in responses among medical professionals and facilities may hinder patients and their relatives from receiving appropriate genetic medical care. Furthermore, MGPT covers genes for which evidence cannot be easily confirmed, making it difficult to stay with the latest findings. Given this current situation, I sincerely hope that this guide will be widely used as a guidepost for medical professionals nationwide, promoting the equalization of medical care throughout Japan for the benefit of patients and their relatives.

It is also encouraging to note the growing number of medical professionals who are passionate about their work, committed to "reduce the number of patients who lose their lives to cancers associated with hereditary cancer syndromes" and to "utilize information obtained from genetic changes for treatment and prevention. Together with these medical professionals, we will strive to provide patients with appropriate medical care based on the latest research findings.

I sincerely hope that this guide will be of use in your medical practice and activities.

March 2025

Arisa Ueki
Editor-in-Chief
"Guidance for hereditary cancer syndrome with Multigene Panel Testing (MGPT)"