Guidelines for the Communication Process in Genomic Medicine

Part 1: Focusing on Comprehensive Tumor Genomic Profiling

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1. Introduction

The significant increase in the rapidity of genomic/genetic analysis using the next-generation sequencing technology has made it possible to analyze many or all genes at a time, and this technology has been applied to routine medical practice. The "Guidelines for Genetic Tests and Diagnoses in Medical Practice" (2011)[1)] by the Japanese Association of Medical Sciences provide the basis for genetic testing, and it is required to adopt a new concept and systems from the perspective of multigene or comprehensive gene analysis in addition to the conventional analysis of a small number of target genes.

Furthermore, although genomic/genetic testing of cancer cells is essentially for somatic mutations, germline mutations (pathogenic variants) are being identified in routine clinical practice; therefore, it is necessary to establish specific approaches for the so-called secondary findings.

Moreover, new effective treatments, such as molecular-targeted drugs and enzyme replacement therapy, are becoming available; however, it is often required to accurately determine the condition of the gens of the target molecule. Such advanced genomic/genetic analysis technologies and treatments are the common property shared by the entire human race, and it is urgently needed to establish a practical application of the medical care using genomic information (genomic medicine) that appropriately links them, so that as many people as possible, including patients' families, can benefit from them with their full understanding.

2. Objective

The objective of the Guidelines is to ensure that healthcare professionals practice communication regarding genomic medicine through an appropriate process in clinical settings, so that patients and their families can fully understand genomic medicine and that the disclosed genomic information will be appropriately used for the medical care and health management of patients and their families. All the concerned parties and organizations, including related academic societies, are required to retain a high level of morality and to respect and appropriately respond to the Guidelines with an accurate understanding of various related issues, so that genomic medicine can be beneficial by gaining the understanding and trust of patients, families, and society.

3. Targets of the Guidelines

The targets of the guidelines will be tests for multiple simultaneous or comprehensive gene analysis using the next-generation sequencing to be conducted as clinical laboratory tests in medical practice. The following two types of tests, which are currently undergoing clinical implementation, are specific targets, but new targets may be added in the future.

I) The so-called tumor profiling (comprehensive tumor genomic profiling; CGP) analysis to be performed for detecting somatic mutations in cancer cells for the diagnosis, treatment, and prognosis of cancer [In comprehensive tumor genomic profiling, only the

tumor tissue is examined, or tumor tissue and germline mutations are tested simultaneously (using normal cells or blood samples). In the former case, if the mutations is suspected to be germline origin,, confirmatory testing is required.. A test (liquid biopsy) using circulating tumor DNA (ctDNA) in blood instead of tumor tissue has also been introduced, but if a germline mutation is suspected that should be disclosed, this test is also required to confirm the mutation, like other tests using tumor tissue alone. The flows concerning secondary findings from these tests are summarized in Appendix Table 1.]. Comprehensive tumor genomic profiling includes comprehensive analyses, such as whole genome sequencing, whole exome sequencing, and gene panel analysis for hundreds of cancer-related genes.

II) Comprehensive analysis of germline, such as whole genome sequencing, whole exome sequencing, and cross-disease gene panel analysis, to be conducted for the diagnosis and treatment of intractable diseases

For the genetic testing to analyze specific genes or gene group in the germline, refer to the "Guidelines for Genetic Tests and Diagnoses in Medical Practice"[1)] by the Japanese Association of Medical Sciences.

In germline gene analyses performed as research, even if the results are disclosed to patients, the Guidelines targeted to medical care exclusively for the diagnosis or treatment, is not applied because the analytical accuracy, means of verification, procedure for disclosure, and financial circumstances are considered to vary widely among researches. However, the Guidelines may also be referred to in the disclosure of the results obtained through research. In addition, it is required to comply with the Ethical Guidelines for Medical and Biological Research Involving Human Subjects.[2)]

4. Basic Concept

The characteristics of germline genetic information are specified in the "Guidelines for Genetic Tests and Diagnoses in Medical Practice" (2011)[1)] by the Japanese Association of Medical Sciences, and special attention shall be paid to the following points among others: They do not change throughout life; they are partially shared among relatives; they may be used to predict the genotypes and phenotypes of relatives at a relatively high probability and to predict future development of diseases almost accurately before onset; and they may cause social disadvantages to the patients and/or their relatives if they are inappropriately handled.

The analytical results obtained by the next-generation sequencing are classified into "primary findings," which are the main objective of the tests, and "secondary findings," which are described below. Although it is necessary to take the time to inform patients of the primary objective of the test in detail, it is also necessary to make sure to explain the possibility of detection of secondary findings and gain their understanding in advance.

Although it is important for all healthcare professionals to follow the patients' intentions and values, for example, the level of information they are seeking, and to proceed with the communication process while confirming their readiness and building their trust, due attention shall be paid to these points particularly in the highly specialized field of genomic medicine.

5. Definition of secondary findings (Note 1)

Conventionally, the term “incidental findings/secondary findings” was often used, but in the Guidelines, we propose to separately refer to obviously pathogenic mutations as “primary findings” if they are the original targets of the test and as “secondary findings” if they are mutations of genes analyzed other than the original targets.

Therefore, the following are defined as secondary findings concerning the targets of the Guidelines:

I) Detection of variants confirmed to be pathogenic in the germline (often described as germline findings in the field of cancer genomic medicine)

II) Detection of variants confirmed to be pathogenic that causes symptoms other than those targeted to be diagnosed

In this case, a mutation confirmed to be pathological is the mutation for which “analytical validity” and “clinical validity” have been established by the “Guidelines for Genetic Tests and Diagnoses in Medical Practice” (2011)[1)] by the Japanese Association of Medical Sciences and, specifically, shall be a truncating loss-of-function mutation (truncating mutation) or definitive pathogenic mutation that has been registered as pathogenic in the ClinVar or other public databases, in principle. However, even information registered in public databases may also be false positive; therefore, information, including clinical information, shall be evaluated by an expert panel in an integrated manner [see 6. (3) below].

6. Specific principles of communication concerning comprehensive tumor genomic profiling

(1) Points of attention in pretest explanation

① Pretest explanation for comprehensive tumor genomic profiling shall be provided primarily by attending physicians, such as experts in cancer chemotherapy, in compliance with the following points of attention. In addition, it is advisable to appoint staff members available to provide supplementary explanation and to have a system in place for patients and their families to receive assistance in order to enhance their understanding based on appropriate explanation.

② When patients and their families are told about cancer and its treatment, they are often barely able to understand the explanation. Therefore, due attention shall be given to the timing of explaining the comprehensive tumor genomic profiling considering the patient’s feelings.

③ Because tests are conducted primarily for the purpose of cancer treatment, an attending physician or specialist experienced in the necessary treatment (cancer chemotherapy, surgery, and radiotherapy, etc.)) shall play a central role in taking the time to provide a detailed pretest explanation. The person who gives explanation shall also provide an appropriate explanation about germline mutations (synonymous to “secondary findings” in comprehensive tumor genomic profiling). The person who gives explanation must also have received appropriate training on how to think about and communicate secondary findings with patients.

④ As there is the possibility of detecting secondary findings, it is desirable that the pretest explanation be given to the patient in the presence of his/her family members, such as his/her spouse or children (This is also desirable from the perspective of cancer treatment. However, the presence of attendants is not mandatory due to time

constraints for cancer treatment, etc. The patient's wishes must be respected with regard to the presence of attendants at the time of disclosure of results.).

⑤ However, prior explanation of secondary findings shall be provided considering the balance with the explanation of the original purpose of the test (The original objective of the test is to treat cancer; therefore, it is preposterous to overemphasize the explanations of secondary findings.).

⑥ After patients have fully understood the explanation, they shall be asked to determine whether or not they wish to disclose any secondary findings that may be beneficial to the health management of the patients and/or their relatives, for which treatment/preventive measures are available, prior to the test in principle (Note 2), and to write their determination accordingly on the consent form. However, it should also be explained to the patient that he/she has the right to remain unaware of secondary findings with full understanding.

⑦ In anticipation of a situation in which it becomes difficult to directly inform the patient of the test results, such as a sudden change in the condition or death, a consent form or a space in the form shall be prepared so that the patient can provide the name and contact information of family members (surrogates) who can be informed of the analytical results if secondary findings are useful for the health management of the patient's relatives (It is desirable that the "family member (surrogate)" whose name and contact information are indicated in the consent form is present at interviews, such as pretest explanation, is informed of the patient's medical condition and comprehensive tumor genomic profiling in advance, and it is also desirable to confirm the member's willingness to be informed. This space may be left blank or be filled in at a later date.).

⑧ It is desirable that the patient's interests, questions, and concerns be first responded to by the healthcare professional involved in cancer treatment and that a system has been established for the patient to seek support from clinical geneticists, certified genetic counselors, etc., as needed, starting from the time of pretest explanation, depending on the factors of concern (e.g., many family histories of cancer and vague anxiety over "cancer family").

⑨ A system (e.g., establishment of a division for clinical genetics and referral system) shall be in place to respond to the needs for genetic counseling that may arise in patients and their families as a result of findings related to germline mutations.

⑩ Because comprehensive tumor genomic profiling is not a substitute for the diagnosis of hereditary tumors, etc., if a hereditary disease such as a hereditary tumor is suspected based on the patient's medical or family history, a test must be conducted to directly analyze the germline separately from the tumor genomic profiling.

⑪ Informed consent shall be obtained from patients after they and their families have fully understood the above information.

⑫ In tumor profiling analysis that examines tumor tissue alone, it should be explained to the patients before the test that a separate confirmatory test is required if there is a presumed germline pathogenic variant (PGPV), for which treatment/preventive measures are available, and which may be beneficial to the health management of the patients and/or their relatives, and consent shall be obtained as to whether they wish to be informed of such secondary findings that are suspected.

⑬ If the patient, such as a child, is deemed incapable of consenting, the explanation shall be given to and consent shall be obtained from an appropriate surrogate, but it is desirable to obtain informed assent according to the patient's ability to understand.

(2) Matters to be explained before the test

① Information concerning cancer that the patient has contracted (e.g., symptoms, treatments (Note 3), and natural history).

② The main objective of this test is to examine genetic changes in cancer cells (somatic mutations).

③ Gene variants that are useful for the treatment of cancer may or may not be found.

④ Even if candidate drugs are found as a result of this analysis, the disease may not be included in the approved indications of existing drugs, or the drugs are unapproved in Japan.

⑤ For the above reason, even if candidate drugs are found, there may be situations in which they are difficult to use for actual treatment for reasons including expensiveness.

⑥ It is possible that the analysis itself ends in failure depending on the quality or quantity of the samples analyzed.

⑦ Approximate results currently obtained concerning ③-⑥are presented.

⑧ The samples used, methods for their collection, organization that analyzes them (if it is located overseas, indicated as such), approximate number of days necessary for the disclosure of the results, and cost of the test.

⑨ The analytical results are interpreted by an expert panel for the evaluation of the treatment plan, and the information is shared among designated core hospitals, designated hospitals and cooperative hospitals of cancer genomic medicine certified by the Japanese government, and may be used as a reference for education of medical workers engaged in cancer treatment and treatment of other patients.

⑩ Germline mutations (synonymous to secondary findings in comprehensive tumor genomic profiling) may be detected with a certain probability (Note 4).3)4)5) However, not all secondary findings can be detected. Thus, the test does not provide results with the same accuracy as a test for the diagnosis of hereditary tumors.

⑪ There may or may not be responsive measures (e.g., treatment/preventive measures) for the expected phenotypes (some are not those of cancer) depending on the secondary findings.

⑫ Secondary findings may affect not only the patients but also their relatives.

⑬ If secondary findings (e.g., genes responsible for hereditary tumors) are detected and considered to be actionable (i.e., treatments/preventive measures are available) and useful for the health management of the patient/relatives, the information can be proactively used. Not using such information may lead to disadvantages. However, the patients and/or their relatives have the right to remain unaware of such information with full understanding. In addition, they are allowed to make or change their decisions at an appropriate timing.

⑭ It is difficult to disclose secondary findings to which responsive measures are unavailable or unknown. [Because analyses using the next-generation sequencing automatically generate an enormous amount of data, it is necessary to select data relevant to the objective of the test (primary findings) and evaluate their accuracy. Although a significant amount of data unrelated to the primary objective of analysis are also generated, it is practically impossible to evaluate all such data (e.g., whether the data are accurate, whether the pathogenicity is plausible).]

⑮ As a large amount of data obtained by comprehensive tumor genomic profiling, including both primary and secondary findings, have been accumulated and expected to contribute to the future development of medicine and welfare of patients, it is desirable that the data be shared among healthcare professionals with strict control of personal information. This also includes sharing of the data in data banks, etc.

⑯ In comprehensive tumor genomic profiling for mutations using tumor tissue alone, a separate confirmatory test is required if a presumed germline pathogenic variant (PGPV) is suspected for which treatment/preventive measures are available, and which may be beneficial to the health management of the patients and/or their relatives. However, patients should be informed that they have the option not to be informed of such suspected secondary findings and not to receive confirmatory tests.

⑰ Even when the test is conducted with the consent of the surrogatesurrogate, it is necessary to respect the patient's future "right to know" and "right to remain unaware" when the patient reaches the stage where he/she is able to make his/her own decisions. At that stage, it is required to ask again if the patient wants to know the test results on hereditary tumors, etc., and if he/she is willing to continue providing data to data banks, and to explain such to his/her surrogate (However, this is intended to ensure that the patient has the opportunity to exercise his/her right to know or remain unaware of the test results again in the future and does not guarantee that the healthcare professional who obtained consent will always provide the patient with an opportunity to reconfirm his/her willingness to do so).

(3) Evaluation of the test results

① To review the individual results of comprehensive tumor genomic profiling in an integrated manner, multidisciplinary conference (expert panel) shall be held on a regular basis with experts including the following: attending physician, experts in cancer chemotherapy, pathologists, experts in genetic medicine, clinical geneticists and certified genetic counselors specialized in genetic counseling, bioinformaticians, experts knowledgeable about molecular genetics and cancer genomic medicine, and pharmacists, nurses, clinical laboratory technicians, and clinical research coordinators (CRCs) engaged in cancer treatment (Note 5).

② In the expert panel, the following points must be reviewed, in principle: (A) Judgment about the analytical validity of the test results (this item may not be included if the test is outsourced); (B) judgment on whether the findings are VUS (variant of uncertain significance) or pathogenic mutations; (C) judgment on whether the findings correspond to primary or secondary findings [judgment on clinical validity by combining (B) and (C)]; (D) judgment on clinical usefulness (evaluation of medical actions such as treatment/preventive measures for the diseases related to the identified pathogenic mutations including primary and secondary findings); and

(E) consideration of ethical, legal, and social viewpoints (methods of disclosing the results and methods of providing medical care) (see Figure 1, Appendix Table 2).

③ The expert panel shall review the contents and points of attention regarding treatment, as well as the provision of information on clinical trials and treatment under appropriate systems, such as clinical studies, advanced medical care, and the patient-requested therapy system when the drug is off-label or unapproved in Japan, responsive measures to be taken when multiple drugs become candidates, and how to communicate the test results (primary findings) to patients (and their surrogates depending on the case).

④ For the items of tumor profiling analysis report to be reviewed by the expert panel, classification by evidence level, and description of treatment selection, refer to the materials including the "Clinical Practice Guidance for Next-Generation Sequencing in Cancer Diagnosis and Treatment" jointly issued by the Japanese Society of Medical Oncology, Japan Society of Clinical Oncology, and the Japanese Cancer Association (Note 6).[6)]

⑤ The primary task of the expert panel is to review primary findings, but for secondary findings, the expert panel shall thoroughly discuss whether there are matters to be disclosed as presented in (4) below, whether confirmatory tests are necessary, what are specific advantages associated with disclosure, and points of attention and method of disclosure while paying attention to different aspects of individual genes. If necessary, discussion shall be held with experts, including the department and other facilities related to the disease involved in the secondary findings.

⑥ If tumor profiling testing using tumor tissue alone yields suspected secondary findings (PGPV) to be disclosed and confirmatory tests of germline mutations are required (Note 7), a system shall be established for implementing or outsourcing the tests.

⑦ If confirmatory tests of germline mutations are required, it is desirable to establish a system that helps reduce increasing burden on patients for this purpose as much as possible (Note 8).

(4) Secondary findings to be considered for disclosure

① Variants highly likely to be pathogenic with a high degree of accuracy, for which clinically established treatment/preventive measures are available with findings beneficial for the health management of the patients and/or their relatives.

② Specifically, truncating loss-of-function mutations or other definitive pathogenic variants registered as "likely pathogenic" or "pathogenic" in ClinVar or other public databases (Note 9).

③ Findings should not be disclosed if they are of insufficient accuracy or certainty, and may cause emotional burden or misunderstanding to the patients and/or their relatives, and if it is not clear that the benefits outweigh the risks.

④ The genes to be disclosed shall be determined by referring to the 73 genes specified by the ACMG (American College of Medical Genetics and Genomics) recommendations,[7)] which are recommended to be disclosed based on the severity of their effects on life and potential for treatment/prophylaxis (Note 9). However, the actionability (e.g., potential for treatment or prophylaxis) in Japan is not comparable

to that in the United States due to differences in the medical care system and other factors. Therefore, the Actionability Working Group-Japan[8] has been releasing Actionability Summary Report in sequence according to the situation in Japan, which is available as reference.

⑤ The findings used for the diagnosis of asymptomatic carriers shall not be disclosed, in principle, as they are not presently considered directly beneficial to the health management of the patients and/or their families.

(5) Points of attention in disclosure of secondary findings

① The wishes about disclosure shall be carefully reconfirmed (Note 2).

② If the patient wishes disclosure in advance, and if no secondary findings to be disclosed are discovered or if no secondary findings to be disclosed are suspected by tumor profiling analysis using tumor tissue alone, the attending physician shall inform the patient accordingly while explaining the results concerning primary findings. It should be noted that no detection or suspicion of secondary findings to be disclosed does not imply the absence of pathological germline mutations. Furthermore, if secondary findings to be disclosed (PGPV) are suspected on tumor profiling analysis using tumor tissue alone, confirmatory tests for secondary findings shall be reexplained and conducted after obtaining informed consent.

③ When secondary findings to be disclosed are determined, the disclosure shall be conducted in a place where privacy is ensured under a system capable of providing adequate genetic counseling with appropriate staff members, including a clinical geneticist and a certified genetic counselor.

④ Collaboration shall be made with departments and specialists inside and outside the facility for diseases involving secondary findings.

⑤ The timing of disclosure of secondary findings does not necessarily have to be simultaneous with the disclosure of primary findings but shall be determined comprehensively considering the therapeutic course and familial history of the patient, as well as the condition of the family (because the significance of surveillance of other organs required by secondary findings may be small for the patient undergoing cancer treatment.).

⑥ Depending on the circumstances, it is necessary to contact the "family member (surrogate) to whom the analytical results may be disclosed if the secondary findings are useful for the health management of relatives" mentioned in the consent form and give genetic counseling to relatives (Note 10) (The secondary findings to be communicated to the "family members (surrogates)" shall be basically the same as the secondary findings to be communicated to the patient.).

(6) Continuous genetic counseling and support for patients, families, and relatives

① For patients from whom secondary findings have been obtained and their relatives, continuous genetic counseling shall be provided at an appropriate timing to ensure that they are involved in periodical surveillance and to promote sharing of information among a wider range of relatives.

② A system shall be established to allow patients to receive genetic testing to examine whether their relatives carry the same mutation (Note 8).

③ Continuous support shall be provided to the patients and their families, for example, by referring them to consultation support centers and psychological support systems (e.g., clinical psychologists and palliative care teams) set up in medical institutions.

7. Specific principles of comprehensive genetic testing for intractable diseases (Note 11)

Irrelevant items shall be deleted by basically following the same concept as "6. Specific principles of comprehensive tumor genomic profiling." However, whole exome sequencing and whole genome sequencing conducted for intractable diseases have different characteristics from comprehensive tumor genomic profiling, such as that the pathogenic significance of detected genetic mutation is unclear in relatively many cases and that secondary findings may be involved in a wide range of disease areas. In most cases, elaborate preparations should be made before disclosing the results, and it will be required to provide adequate genetic counseling and to provide new medical services and referrals, which will require additional fees to be charged, if secondary findings are discovered and requested to be disclosed. Therefore, separate guidelines have been established for comprehensive genetic testing for intractable diseases (Note 12).

8. Preparation of conditions for a more appropriate implementation of genomic medicine systems, including responsive measures to secondary findings

① Shall be able to provide confirmatory testing for germline mutations, such as the ACMG73 gene[7)], for which treatment/preventive measures are available as medical services (specifically, facilities shall be in place to provide the tests, and the test shall be available at appropriate expenses through public health insurance and benefits for advanced medical services).

② Such tests shall be adequately accurate.

③ Population-specific databases shall be improved so that the pathological significance of detected mutations can be correctly determined.

④ Genetic counseling system shall be improved as a standard medical service.

⑤ Proactive training opportunities shall be provided from a medium- to long-term perspective for highly specialized human resources who will assume responsibility for genetic counseling and genome informatics.

⑥ Legislation shall be implemented to explicitly prohibit discrimination based on genetic and genomic information.

⑦ Genomic information shall be securely managed and appropriately shared among medical staffs as the basic information for medical care.

⑧ Healthcare professionals involved in genomic medicine shall not only deliver accurate and comprehensible information on genomic medicine to patients, their families, and the general public but also keep in mind to engage in interactive communication by receiving feedback from patients, their families, and the general public.

The above-listed systems shall be developed separately from the Guidelines as a prerequisite of society/medical care.

9. Other tasks

Matters not mentioned in the Guidelines shall be handled by referring to the Guidance for Appropriate Handling of Personal Information by Medical and Care Services (April 14, 2017) (https://www.mhlw.go.jp/file/06-Seisakujouhou-12600000-Seisakutoukatsukan/0000194232.pdf) and in compliance with relevant laws and regulations.

(Note 1) Conventionally, the term "incidental findings/secondary findings" was often used, but in the Guidelines, we propose to separately refer to obviously pathogenic mutations as "primary findings" if they are the original targets of the test and as "secondary findings" if they are genes to be analyzed for other purposes than the original ones. This is because the term "incidental findings" may raise the image that the variants are out of the targets of the analysis, and may lead to less awareness of the variants and/or retarded action. This definition of "secondary findings" slightly differs from the definition in the report by the Presidential Commission for the Study of Bioethical Issues[9] or by the ACMG.[10] According to the report by the Presidential Commission for the Study of Bioethical Issues, "secondary findings" are described as "Practitioner aims to discover A, and also actively seeks D per expert recommendation" mentioning that "ACMG recommends that laboratories conducting large-scale genetic sequencing for any clinical purpose should look for variants underlying 24 phenotypic traits" as an example. The ACMG recommendations[10] require separate assessment of 56 genes (presently 73 genes[7]) unless the patient opts out, and pathogenic variants detected under these conditions are termed "secondary findings." Therefore, "secondary findings" defined by the ACMG are considered to mean only those with available treatments/preventive measures and should be disclosed. In Japan, however, the same definition of "secondary findings" as that in the United States cannot be adopted as it is still premature to define the ACMG73 genes[7] as actionable, and the actionability varies under different situations. "Secondary findings," as defined here, shall include findings for which treatment/preventive measures are available and should be disclosed and findings which should not be disclosed. After accepting these conditions, it is necessary for the expert panel to discuss and carefully determine whether they should be disclosed. In addition, treatment for hereditary breast and ovarian cancer syndrome based on the results of genetic diagnosis and treatment using the results of microsatellite instability testing, which can also be a screening test for Lynch syndrome, have started, and germline mutations detected by these tests are close to primary findings for treatment and are more important than other secondary findings. Thus, it is also important to keep in mind the fact that the definition of hereditary tumor as secondary findings in comprehensive tumor genomic profiling is becoming vague. However, as it is troublesome to consistently use the expression "pathogenic germline mutations detected by comprehensive tumor genomic profiling," we propose to them to be termed "secondary findings" to facilitate communication among designated core hospitals, designated hospitals and cooperative hospitals of cancer genomic medicine throughout Japan.

(Note 2) The patients shall be asked about their wishes to disclose secondary findings before the testimg and confirmed before disclosure, in principle, but it shall also be allowed to confirm their wishes by the time of disclosure without requiring final decision-making before comprehensive tumor genomic profiling. In addition, it is also required to remind the patients that they have the right to withdraw consent. If a germline mutation (PGPV) is suspected by tumor profiling analysis using tumor tissue alone, thus requiring a confirmatory test, it shall be necessary to reconfirm the patient's wishes about the confirmatory test at an appropriate timing, for example, when disclosing primary findings. In this case, it is desirable for a

clinical geneticist or a certified genetic counselor to cooperate in the explanation to the patient.

(Note 3) It shall be necessary to provide an explanation including information concerning the current cancer medication (e.g., information concerning drugs covered by public health insurance and state of clinical trials of drugs not approved in Japan).

(Note 4) In general, when comprehensive tumor genomic profiling is conducted, germline mutations are reportedly detected at a rate of a few percent,[3)4)5)] but the frequency of germline mutation detection varies among cancer types and populations. For example, in ovarian cancer, including fallopian tube cancer and peritoneal cancer, germline mutations of *BRCA1* or *BRCA2* are detected at a frequency of 11.7% in Japanese and 29.0% in Ashkenazi Jews,[11)12)] and there is the possibility of identifying germline mutations latently present in such cancers by comprehensive tumor genomic profiling.

(Note 5) For the members of the expert panel, refer to the "Guidelines for Establishing Designated Core Hospitals of Cancer Genomic Medicine." In addition, see Figure 1 and Appendix Table 2 for the members and their roles.

(Note 6) The Guidelines focus on the communication process in genomic medicine; therefore, the "Clinical Practice Guidance for Next-Generation Sequencing in Cancer Diagnosis and Treatment"[6)] jointly issued by the Japanese Society of Medical Oncology, Japan Society of Clinical Oncology, and the Japanese Cancer Association should be referred to for the overview of cancer diagnosis and treatment based on comprehensive tumor genomic profiling.

(Note 7) In comprehensive tumor genomic profiling, mutations are investigated in tumor tissue alone or simultaneously in tumor tissue and germline (using normal cells and/or blood samples).

In the former case, the possibility of germline mutations is comprehensively evaluated according to the information such as gene name, variants identified as germline founder mutations, age of onset, history of present illness, past history, familial history, allele frequency, and percentage of tumor cells.[13)] The "Comprehensive Tumor Genomic Profiling: Materials for Review of Secondary Findings, Ver. 1.0" [Comprehensive Tumor Genomic Profiling: List of secondary findings to be disclosed to patients by the level of recommendation; Operational guidelines and guidance for germline confirmatory testing of secondary findings in comprehensive tumor genomic profiling using tumor tisuue alone; and Operational guidelines and guidance for germline confirmatory testing of secondary findings in comprehensive tumor genomic profiling (liquid biopsy) using circulating tumor DNA in blood] can be used as a reference for the evaluation. If a germline mutation (PGPV) is suspected, it is necessary to conduct a test to confirm it. On the other hand, when mutations are investigated simultaneously in tumor tissue and germline, retesting is not required, in principle, if the analysis is conducted with controlled accuracy. However, if the analysis does not have a certain level of accuracy control, a confirmatory test is required.

(Note 8) If comprehensive tumor genomic profiling is covered by public health insurance, it is permitted to include additional fees for hereditary tumor counseling when disclosing the results. However, there are problems to be solved in the system as clinical practice, for example, confirmatory tests for PGPV of the patient, and genetic counseling and /or genetic testing separately provided to the patient's relatives (6. (6) ① ②), are not covered by public health insurance in most cases at this time.

(Note 9) The handling of likely pathogenic variants shall be carefully reviewed by the expert panel. The ACMG guidelines[14)] should also be referred to for the evaluation of variants. In addition, as nonsense/frameshift mutations occurring near the C-terminal of protein, even if they seem to be truncating loss-of-function mutations, may not be considered pathogenic, the mutations need to be variants on the 5'-terminal side rather than the variants established as definitively pathogenic missense variants. Consideration shall be given to individually disclosing genes for which the management methods have been proposed in various guidelines.

(Note 10) For secondary findings useful for the health management of the patient's relatives, such findings shall be first communicated by the patient to their relatives, in principle, but it shall also be necessary for the medical staff to communicate such findings to the relatives depending on the patient's medical condition. In this case, the decision as to whether the family member (surrogate) should be contacted by the attending physician of the relevant department or the genetic counseling division shall be made on a case-by-case basis, considering the relationship between the medical staff and the patient or his/her family member (surrogate) and the necessity of explaining the patient's medical condition.

(Note 11) The Guidelines are not intended to be directly applied to germline multi-gene panel analysis of disease groups (which usually analyzes several tens to several hundreds of genes), as it is conceptually considered to yield no secondary findings. However, it is possible for mutations to be discovered in initially unexpected genes germline multi-gene panel that includes a large number of genes; therefore, the concept of the Guidelines may be used as a reference.

(Note 12) Refer to the "Guidelines for the Communication Process in Genomic Medicine. Part 2: Specific principles of comprehensive germline genetic analysis using next-generation sequencing."

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Change log

1. First edition: Proposal concerning the process of information transmission in genomic medicine –Comprehensive tumor genomic profiling and germline whole genome/whole exome sequencing– [First edition] (March 21, 2018)
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Research Project on Ethical, Legal, and Social Issues Supported by the Health, Labour and Welfare Sciences Research Grants

"Extraction of ethical and social issues and improvement of social environment toward the realization of a society where people can benefit from genome medicine without anxiety"

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Appendix Table 1: Flow of Informed Consent Related to Secondary Findings in Comprehensive Tumor Genomic Profiling

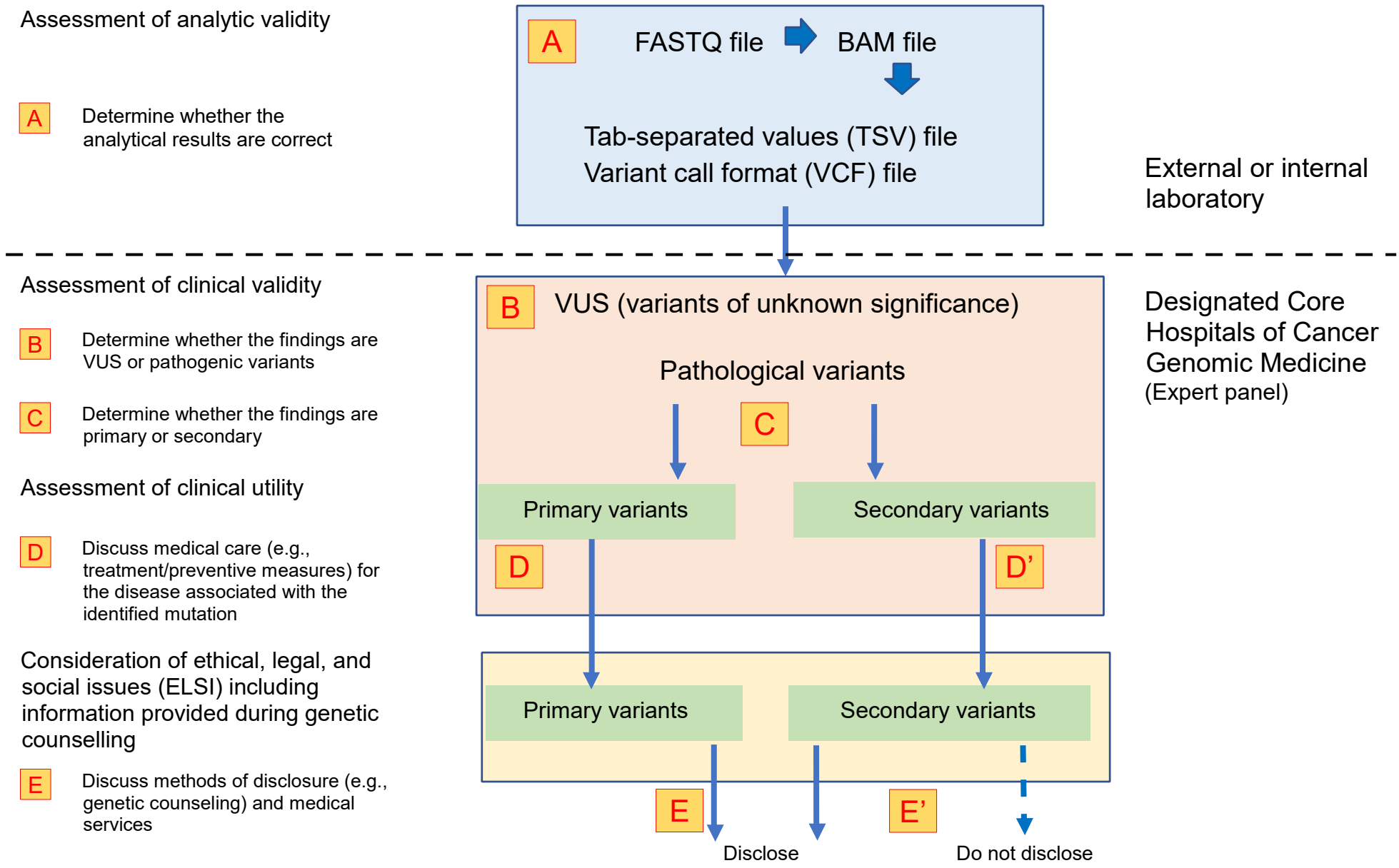
T/N-pair panel: A panel enabling simultaneous testing of mutations in tumor tissues and germline (e.g., by testing normal cells and collecting blood)

T-only panel: A panel to test tumor tissues alone

	T/N-pair panel	T-only panel
Pretest explanation	Secondary findings* may be identified	Suspected secondary findings (PGPV) may be identified Additional confirmatory testing is required to confirm the secondary findings
Pretest consent	Does the patient wish to be informed about the secondary findings?	Does the patient wish to be informed about the suspected secondary findings?
Testing	To be performed on tumor tissues and blood	To be performed on tumor tissue only
Expert panel	Are there any secondary findings?	Are there any suspected secondary findings? Is a confirmatory test feasible?
Disclosure	Primary and secondary findings (not to be disclosed simultaneously)	There are suspected secondary findings
Consent at disclosure		Is the patient tested to confirm the secondary findings?
Confirmatory testing		To be performed on collected blood
Disclosure		Secondary findings

*In this context, "secondary findings" refer to findings that should be disclosed to patients (i.e., medically actionable findings).

Appendix Figure 1. Flow for data obtained in the NGS panel



Appendix Table 2. Members of the cancer genomics expert panel and their roles
◎: Core member, ○: Participation ideal, △: circumstantial

Process	Requirement for expert panel on Guidelines for Establishing Designated Core Hospitals of Cancer Genomic Medicine. II21(2)②d(*): indicates that participation in the expert panel is not required but ideal	(a) Experts in cancer drug therapy	(b) Experts in genetic medicine	(c) Genetic counselors	(d) Pathologists	(e) Expert in cancer genomics medicine#	(f) Bioinformatician	(g) Attending physician	*Assistant coordinator for genetic counseling	*CRC*	*Nurses involved in cancer treatment*	*Pharmacists involved in cancer treatment*	*Clinical laboratory technicians and clinical laboratory physicians involved in cancer treatment*
	Requirement by Designated Core Hospitals of Cancer Genomic Medicine	○	○	○	○	○	○	○	○				
A	To determine the accuracy of the analytical results	○			○	○	◎						○
B	To determine whether the findings are VUS or pathogenic variants	○	○	○		◎	○						
C	To determine whether the findings are primary or secondary	○	◎	○	△*	○		○					
D	To discuss medical care (e.g., treatment/preventive measures) for the disease associated with the identified mutation	◎	○	○		○		○				○	
E	To discuss methods of disclosure (e.g., genetic counseling) and appropriate medical services	○	○	◎		○		○	○		○		

experts knowledgeable about molecular genetics and cancer genomic medicine
* If the initial test was limited to tumor tissue, additional analyses (e.g., ratio of tumor cells) are required to assess secondary findings.

Guidelines for the Communication Process in Genomic Medicine

Part 2: Specific principles of comprehensive germline genetic analysis using next-generation sequencing

[Revised 2nd edition]

08/09/2021

The Guidelines aim to address issues during comprehensive germline genetic analysis using next-generation sequencing or other techniques to be conducted as a clinical laboratory test. However, as of 2021, germline genetic analysis have been conducted in Japan as laboratory tests for only 147 diseases covered by public health insurance and approximately 200 diseases, including those treated with advanced medical care or non-insured medical care. In Japan, comprehensive germline genetic analysis, such as whole-exome/whole-genome sequencing using the next-generation sequencing, has been performed almost exclusively for research purposes so far.

In the United States and other countries, comprehensive analytical tests, such as germline whole-exome analysis, have been conducted as laboratory tests for more than several years. In light of this situation, it is important to consider how to address future issues in Japan as well. Currently, in Japan, we are steadily promoting the Action Plan for Whole-Genome Analysis based on the principles of “Patient-initiated and patient-returned medicine” and developing a system that enables industry, government, and academia to widely analyze and utilize data in order to provide new personalized medical care to patients for whom no treatment has been available so far.

Comprehensive germline genetic analysis conducted for the diagnosis of patients suspected to have hereditary diseases has characteristics different from those of comprehensive tumor genomic profiling such as that the pathogenic significance of detected variants (base sequences with deviations from the reference sequence) remains unclear in relatively many cases and that secondary findings may be involved in a wide range (Note 1) of disease areas. Careful preparations should be made before disclosing the results, and it will be required to provide adequate genetic counseling, as well as to provide new medical services and referrals to specialists in the relevant disease area, if secondary findings are discovered and requested to be disclosed.

The idea of comprehensive germline genetic analysis was hardly conceived at the time when the Guidelines for Genetic Tests and Diagnoses in Medical Practice by the Japanese Association of Medical Sciences (http://jams.med.or.jp/guideline/genetics-diagnosis.pdf) were prepared (2011). Although it is significantly different in nature from comprehensive tumor genomic profiling, comprehensive germline genetic analysis is expected to develop as an important examination in all areas of medicine. Therefore, all parties and organizations concerned, including related academic societies, are required to retain a high level of morality and to respect and appropriately respond to the Guidelines with an accurate understanding of various related issues, so that genomic medicine can be beneficial by gaining the understanding and trust of patients, families, and society.

(1) Comprehensive germline genetic analysis using next-generation sequencing targeted by the Guidelines (Note 2)

Comprehensive germline genetic analysis is to be conducted at medical institutions or registered clinical laboratories as a laboratory test for diagnosis and treatment purposes as per the Medical Care Act and the 2 usually under public health insurance but occasionally as a non-insured medical service including advanced medical care.

① Whole-genome analysis, such as whole-genome sequencing, performed as a clinical laboratory test

② Whole-exome analysis performed as a clinical laboratory test

③ Cross-disease group panel analysis to be performed as a clinical laboratory test

④ When the results of analyses corresponding to ①-③ above performed as part of research are confirmed as clinical laboratory test results and disclosed to the patient

As the results of human genome/gene analysis researches belong to the subjects, they may be returned to the subjects depending on the content of the informed consent. However, as they are not the results of clinical laboratory tests, they must be carefully and appropriately handled paying attention to the fact that quality control required for their use in clinical practice is not systematically implemented. It is particularly important to have the subjects understand the limitations of research. The intent of the Guidelines shall be referred to when returning the results of such a research to the subjects. The "Returning Results of Personal Genetic Information in Research: Recommendations for Matters to Review and Consider, and Issues for Future Discussion and Review" (https://www.amed.go.jp/content/000048196.pdf) shall also be referred to.

(2) Points of attention in testing

① To conduct comprehensive genetic analysis, it is necessary to establish a medical genetics section (an organization with a system for genetic counseling collaborating with other clinical departments). The requirements for setting up a medical genetics section should include the following: the section has a certified genetic counselor and multiple clinical genetic specialists working as full-time staff members; conferences are held on a regular basis in collaboration with the medical genetics section; the section has a facility for training on the clinical genetic specialist system; and the section is affiliated with the National Liaison Council for Clinical Sections of Medical Genetics.

② As clinical information is highly important in interpreting the results of comprehensive germline genetic analysis, it is required, in principle, to collect a sufficient amount of necessary clinical information, including the results of other laboratory tests, and conduct available general genetic examinations (e.g., chromosome tests, tests of candidate genes, and disease group panel tests) before deciding to conduct comprehensive germline genetic analysis. However, a flexible approach should be taken, as it may be more efficient to conduct a comprehensive analysis from the beginning depending on the situation.

③ The primary objective of the analysis is to establish a previously unknown diagnosis, but as the analytical results are information that can also be shared by the patient's relatives, a pretest explanation shall be provided by taking sufficient time in close

cooperation with the attending physician or specialist in the patient's symptoms and experts in genetic medicine, such as clinical geneticists and certified genetic counselors, and an appropriate explanation about secondary findings shall also be provided.

④ As it is possible that primary findings affect the health condition, health management, or reproductive behavior of the patient's relatives and that secondary findings are discovered, and because analyses may be conducted not only for the patients but also simultaneously for their parents and siblings, it is desirable to appropriately provide information to attendants such as the family members, including their parents and siblings.

⑤ However, prior explanation of secondary findings shall be provided considering the balance with the explanation of the original purpose of the test (The original objective of the test is to diagnose the present disease; therefore, it is preposterous to overemphasize the explanations of secondary findings.).

⑥ After sufficiently explained to the patient, they shall be asked to determine whether or not they wish to disclose any secondary findings that may be beneficial to the health management of the patients and/or their relatives, for which treatment/preventive measures are available, prior to the test in principle (Note 3), and to write their determination accordingly on the consent form. However, it should also be explained to the patient that he/she has the right to remain unaware of secondary findings with full understanding.

⑦ In anticipation of a situation in which it becomes difficult to directly inform the patient of the test results, such as a sudden change in the condition or death, it is desirable that a consent form or a space in the form shall be prepared so that the patient can provide the name and contact information of family members (surrogates) who can be informed of the analytical results if secondary findings are useful for the health management of the patient's relatives (It is desirable that the "family member (surrogate)" whose name and contact information are indicated in the consent form is present at interviews, such as pretest explanation, is informed of the patient's medical condition and comprehensive germline genetic analysis in advance, and it is also desirable to confirm the member's willingness to be informed. This space may be left blank or be filled in at a later date.).

⑧ Informed consent shall be obtained from patients after they and their families have fully understood the above information.

⑨ In addition to the aforementioned aspects, comprehensive germline genetic analysis is considered to have a significant psychosocial impact because the probability of obtaining primary results is not necessarily high, definitive results may not always be obtained, and the parents may turn out to be presymptomatic or asymptomatic mutation carriers. In addition to these, it is important to provide pretest genetic counseling to discuss the reasons for wishing to be tested and expectations for the test.

⑩ If the patient, such as a child, is deemed incapable of consenting, the explanation shall be given to and consent shall be obtained from an appropriate surrogate, but it is desirable to obtain informed assent according to the patient's ability to understand.

(3) Matters to be explained before the test

① Review of the time course and results of tests conducted so far, time course of diagnostic process adopted by the attending physician, and reasons for proposing comprehensive genetic analysis

② This analysis is aimed primarily at finding the cause of the present symptoms and to establish the diagnosis

③ Possibility (and probability) that the pathogenic mutation (pathogenic variant) responsible for the present symptoms is discovered or not (Note 4)

④ Establishment of the diagnosis is essential for medical practice, and comprehensive genetic analysis is an important examination as required from the medical practice perspective. However, even if the pathogenic variant responsible for the present symptoms is found, the finding may not immediately lead to treatment or clarification of the future health management method or natural history and may seriously affect the life prognosis.

⑤ In addition, although the pathogenic significance should be evaluated with maximum effort at present and based on the latest information, interpretations may change at a later date as new findings accumulate over time with the development of research.

⑥ Additional laboratory tests may be necessary depending on the detected variant, such as when it is a previously unreported or scarcely reported variant. Furthermore, it may be necessary to determine as to whether the variant is truly responsible for the disease according to the results of future studies.

⑦ In some cases, it may be important to simultaneously analyze and compare the results from the patient's relatives, including parents and siblings, to evaluate the pathogenic significance of many variants.

⑧ As major structural change or large deletion may not be detected due to technical limitations of next-generation sequencing, genetic diseases should not be ruled out due to the absence of primary findings.

⑨ The discovered primary findings (mutation responsible for the disease) may have been shared by the relatives and may affect their health condition, health management, and reproductive behavior.

⑩ Pathogenic variants seemingly unrelated to the present symptoms (secondary findings) may be detected with a certain probability (Note 5). However, not all secondary findings can be detected.

⑪ There may or may not be responsive measures (e.g., treatment/preventive measures) for the expected phenotypes depending on secondary findings.

⑫ Secondary findings may affect not only the patients but also their relatives.

⑬ If secondary findings (e.g., hereditary tumor or cardiovascular disease) are discovered and considered to be actionable (i.e., treatment/preventive measures are available) and useful for the health management of the patient/relatives, the information can be proactively used. Not using such information may lead to disadvantages. However, the patients and/or their relatives have the right to remain

unaware of such information with full understanding. In addition, they are allowed to make or change their decisions at an appropriate timing.

⑭ It is difficult to disclose secondary findings for which responsive measures are unavailable or unknown [Because analyses using next-generation sequencing automatically generate an enormous amount of data, it is necessary to select data relevant to the objective of the test (primary findings) and evaluate their accuracy. Although a significant amount of data unrelated to the primary objective of analysis are also generated, it is practically impossible to evaluate all such data (e.g., whether the data are accurate, whether the pathogenicity is plausible).].

⑮ As a large amount of data obtained by comprehensive germline genetic analysis, including both primary and secondary findings, have been accumulated and expected to contribute to the future development of medicine and welfare of patients, it is desirable that the data be shared among healthcare professionals with strict control of personal information.

⑯ In some cases, it is difficult to determine whether the discovered findings are primary findings responsible for the disease to be diagnosed or secondary findings unrelated to the disease.

⑰ If the patient is a child and if a secondary finding related to a late-onset actionable disease necessity may arise to fully discuss the psychosocial impact of disclosing the information as there is no direct medical benefit to the child, even if the information is beneficial to the parents or relatives.

⑱ Even when the test is conducted with the consent of the surrogate, it is necessary to respect the patient's future "right to know" and "right to remain unaware" when the patient reaches the stage where he/she is able to make his/her own decisions. At that stage, it is required to ask again if the patient wants to know the test results on secondary findings, and if he/she is willing to continue providing data to data banks, and to explain such to his/her surrogate (However, this is intended to ensure that the patient has the opportunity to exercise his/her right to know or remain unaware of the test results again in the future and does not guarantee that the healthcare professional who obtained consent will always provide the patient with an opportunity to reconfirm his/her willingness to do so).

⑲ In some cases, test results (primary and secondary findings) may have a psychological impact on the subjects and their families. It is advisable to provide anticipatory guidance (Note 6) or discussion in response to the test results as part of pretest genetic counseling (Note 7).

⑳ If the results analyzed for research purposes (primary and secondary findings) are to be used for clinical practice as laboratory test results, it shall be explained to the subject that confirmatory testing will be considered in accordance with the Guidelines before participating in the study. In principle, a confirmatory test shall be conducted after re-collecting blood, and at that time, the subject shall be asked to give his/her consent to the test.

(4) Evaluation of the test results

① It is advisable to hold conferences (expert panels) in collaboration between the relevant clinical department and the medical genetics section on a regular basis with the attending physician, experts in the clinical field, and those who versed in the interpretation of the results of genetic testing, such as clinical geneticists and certified genetic counselors specialized in genetic medicine/genetic counseling, as mandatory members and to comprehensively evaluate the individual results of comprehensive germline gene analyses among the participants. If necessary, experts in genetic testing in the specific field, analysts in charge of the actual genomic analysis, bioinformaticians involved in the relevant genomic analysis (e.g., genetic expert), nurses, and clinical laboratory technicians shall be invited to the conference. Because it may well be impossible for a single institution to organize an expert panel including experts in the area related to the secondary findings, it is important to establish a local or nationwide organization or network capable of reviewing the results of comprehensive germline genetic analysis.

② In the expert panel, the following points must be reviewed, in principle: (A) Judgment about the analytical validity of the test results (this item may not be included if the test is outsourced); (B) judgment on whether the findings are VUS (variant of uncertain significance) or pathogenic mutations; (C) judgment on whether the findings correspond to primary or secondary findings [judgment on clinical validity by combining (B) and (C)]; (D) judgment on clinical usefulness (evaluation of medical actions such as treatment/preventive measures for the diseases related to the identified pathogenic mutations including primary and secondary findings); and (E) consideration of ethical, legal, and social viewpoints (methods of disclosing the results and methods of providing medical care) (see Figure 1).

③ The expert panel shall also discuss how to communicate the test results (primary findings) to the patients (or their surrogates depending on the case) and their relatives.

④ The primary task of the expert panel is to review primary findings, but for secondary findings, the expert panel shall thoroughly discuss whether there are matters to be disclosed as presented in (5) below, whether confirmatory tests are necessary, what are specific advantages associated with disclosure, and points of attention and method of disclosure while paying attention to different aspects of individual genes. If necessary, discussion shall be held with experts, including the department and other facilities related to the disease involved in the secondary findings.

⑤ When the results of analysis conducted for research purposes (primary and secondary findings) are to be disclosed as laboratory test results, it is necessary, in principle, to perform confirmatory tests at a clinical laboratory using newly collected blood samples.

(5) Secondary findings to be considered for disclosure

① Variants highly likely to be pathogenic with a high degree of accuracy, for which clinically established treatment/preventive measures are available with findings beneficial for the health management of the patients and/or their relatives.

② Specifically, truncating loss-of-function mutations or other pathogenic variants registered as “likely pathogenic” or “pathogenic” in ClinVar or other public databases (Note 8).

③ Findings should not be disclosed if they are of insufficient accuracy or certainty, and may cause emotional burden or misunderstanding to the patients and/or their relatives, and if it is not clear that the benefits outweigh the risks.

④ The genes to be disclosed shall be determined by referring to the 73 genes specified by the ACMG (American College of Medical Genetics and Genomics) recommendations,[1)] which are recommended to be disclosed based on the severity of their effects on life and potential for treatment/prophylaxis. However, the actionability (e.g., potential for treatment or prophylaxis) in Japan is not comparable to that in the United States due to differences in the medical care system and other factors. Therefore, the Actionability Working Group-Japan (http://www.idenshiiryoubumon.org/actionability_japan/index.html) has been releasing Actionability Summary Report in sequence according to the situation in Japan, which is available as reference.

⑤ Even if the discovered findings can be used for the diagnosis of asymptomatic carriers, they shall not be disclosed, in principle, as they are not presently considered directly beneficial to the health management of the patients and/or their families.

(6) Points of attention in disclosure of primary findings

① The patient’s wishes about disclosure of the results shall be confirmed.

② The results shall be disclosed in close collaboration among the attending physician or an expert specialized in the patient’s symptoms and specialists in genetic medicine, such as a clinical geneticist and certified genetic counselor.

③ The significance of the results for the patient and his/her relatives shall be explained in detail.

(7) Points of attention in disclosure of secondary findings

① The wishes about disclosure shall be carefully reconfirmed (Note 3).

② If the patient wishes disclosure in advance, and if no secondary findings to be disclosed are discovered, the patient shall be informed accordingly while explaining primary findings. It should be noted that no detection f secondary findings to be disclosed does not imply the absence of secondary findings.

③ When secondary findings to be disclosed are found, the disclosure shall be conducted in a place where privacy is ensured under a system capable of providing adequate genetic counseling with appropriate staff members, including a clinical geneticist and a certified genetic counselor.

④ Collaboration shall be made with departments and specialists inside and outside the facility for diseases involving secondary findings. In particular, if the institution has no relevant specialist, collaboration shall be made between the attending physician who initiated the test and medical organizations involved in the secondary findings

through a certified genetic counselor of the medical genetics section while using information from the network for intractable disease care.

⑤ Depending on the circumstances, it is necessary to contact the "family member (surrogate) to whom the analytical results may be disclosed if the secondary findings are useful for the health management of relatives" mentioned in the consent form and give genetic counseling to relatives (Note 9).

(8) Continuous genetic counseling and support for patients, families, and relatives

① For patients from whom primary and secondary findings have been obtained and their relatives, continuous genetic counseling shall be provided at an appropriate timing to ensure that they are involved in periodical surveillance and to promote sharing of information among a wider range of relatives.

② A system shall be established to allow patients to receive genetic testing to examine whether their relatives carry the same mutation.

(9) Other

The Guidelines are not intended to be directly applied to germline multi-gene panel analysis of disease groups (which usually analyzes several tens to several hundreds of genes), as it is conceptually considered to yield no secondary findings. However, it is possible for mutations to be discovered in initially unexpected genes germline multi-gene panel that includes a large number of genes; therefore, the concept of the Guidelines may be used as a reference.

The specific design of genetic counseling associated with comprehensive germline gene analysis will be further reviewed, and the results will be added to the Guidelines.

Matters not mentioned in the Guidelines shall be handled by referring to the Guidance for Appropriate Handling of Personal Information by Medical and Care Services (April 14, 2017) (https://www.mhlw.go.jp/file/06-Seisakujouhou-12600000-Seisakutoukatsukan/0000194232.pdf) and in compliance with relevant laws and regulations.

The results of comprehensive germline genetic analysis conducted for research purposes shall be returned to the subjects by referring to the "Ethical Guidelines for Medical and Biological Research Involving Human Subjects" and the "Returning Results of Personal Genetic Information in Research: Recommendations for Matters to Review and Consider and Issues for Future Discussion and Review" (https://www.amed.go.jp/content/000048196.pdf).

(10) Preparation of conditions for a more appropriate implementation of genomic medicine systems, including responsive measures to secondary findings

① Shall be able to provide confirmatory testing for germline mutations, such as the ACMG73 gene[1)], for which treatment/preventive measures are available as medical services (specifically, facilities shall be in place to provide the tests, and the test shall be available at appropriate expenses through public health insurance and benefits for advanced medical services).

② Such tests shall be adequately accurate.

③ Population-specific databases shall be improved so that the pathological significance of detected mutations can be correctly determined.

④ Genetic counseling system shall be improved as a standard medical service.

⑤ Proactive training opportunities shall be provided from a medium- to long-term perspective for highly specialized human resources who will assume responsibility for genetic counseling and genome informatics.

⑥ Legislation shall be implemented to explicitly prohibit discrimination based on genetic and genomic information.

⑦ Genomic information shall be securely managed and appropriately shared among medical staffs as the basic information for medical care.

⑧ Healthcare professionals involved in genomic medicine shall not only deliver accurate and comprehensible information on genomic medicine to patients, their families, and the general public but also keep in mind to engage in interactive communication by receiving feedback from patients, their families, and the general public.

The above-listed systems shall be developed separately from the Guidelines as a prerequisite of society/medical care.

(Note 1) Conventionally, the term "incidental findings/secondary findings" was often used, but in the Guidelines, we propose to separately refer to obviously pathogenic mutations as "primary findings" if they are the original targets of the test and as "secondary findings" if they are genes to be analyzed for other purposes than the original ones. This is because the term "incidental findings" may raise the image that the variants are out of the targets of the analysis, and may lead to less awareness of the variants and/or retarded action. This definition of "secondary findings" slightly differs from the definition in the report by the Presidential Commission for the Study of Bioethical Issues[2] or by the ACMG.[3] According to the report by the Presidential Commission for the Study of Bioethical Issues, "secondary findings" are described as "Practitioner aims to discover A, and also actively seeks D per expert recommendation" mentioning that "ACMG recommends that laboratories conducting large-scale genetic sequencing for any clinical purpose should look for variants underlying 24 phenotypic traits" as an example. The ACMG recommendations[3] require separate assessment of 56 genes (presently 73 genes[1]) unless the patient opts out, and pathogenic variants detected under these conditions are termed "secondary findings." Therefore, "secondary findings" defined by the ACMG are considered to mean only those with available treatments/preventive measures and should be disclosed. In Japan, however, the same definition of "secondary findings" as that in the United States cannot be adopted as it is still premature to define the ACMG73 genes[1] as actionable, and the actionability varies under different situations. "Secondary findings," as defined here, shall include findings for which treatment/preventive measures are available and should be disclosed and findings which should not be disclosed. After accepting these conditions, it is necessary for the expert panel to discuss and carefully determine whether they should be disclosed.

(Note 2) The Guidelines shall not apply to prenatal diagnosis or diagnosis of embryonic tissue.

(Note 3) The patients shall be asked about their wishes to disclose secondary findings before testing. It is also required to remind the patients that they have the right to withdraw consent. Even in an analysis as part of research, it is desirable to confirm beforehand whether the patient wishes to receive a confirmatory test in case secondary findings are suspected and a confirmatory test as a laboratory test is required.

(Note 4) In general, the diagnostic rate is reported to be approximately 25%–40% by whole-exome analysis and 50% by whole-genome analysis.[4)] The frequency of detection of germline mutations varies depending on the symptoms to be diagnosed, subject population, presence of family history, and interpretation method of pathogenic significance.

(Note 5) Germline mutations corresponding to secondary findings are reportedly detected at an overall frequency of a few percent by whole-exome analysis, but the frequency varies depending on the definition of secondary findings and interpretation method of pathologic significance.[5)-12)]

(Note 6) Anticipatory guidance: Before the test, have the subjects think about anticipated changes in their feelings when they are informed of the test results, and what specific measures should be taken to cope with such changes.

(Note 7) Presently, comprehensive germline gene analysis is often conducted on patients suspected to have an undiagnosed genetic disease. Studies have demonstrated that if a pathogenic variant is detected and the diagnosis is established, the patient is freed from long-standing search for the cause (search for the diagnosis) (“end of diagnostic odyssey”), which leads to elucidation of future prospects and a sense of relief and security. On the other hand, there are reports of cases where the patients experience psychological burden, difficulty in adapting to the new diagnosis, and loss of the previous peer network (network with persons with the same disease or in a similar situation) due to the established condition as a genetic disease and prognostic information. Some studies also reported that they feel it is not necessarily the end of “diagnostic odyssey” but the beginning of a new “odyssey.” Moreover, it is important to further investigate the psychosocial effects of cases where no pathogenic variant is detected or the test results are ambiguous, and for the moment, it is essential to provide continued genetic counseling after explaining the results regardless of what they are.[4),13)-15)] Specifically, some patients and families may be psychologically shocked, whereas others may be relieved by knowing their pathogenic variants. On the other hand, some may be relieved, whereas others may be disturbed if no pathogenic variants are detected. In addition, with regard to secondary findings, there are cases where friction occurs in the family as to whether the patient should receive the test or how to communicate the test or results, and the patient feels survivor’s guilt (sense of guilt felt by having survived or not being ill).

(Note 8) The handling of likely pathogenic variants shall be carefully reviewed by the expert panel. The ACMG guidelines[16)] should also be referred to for the evaluation of variants. In addition, as nonsense/frameshift mutations occurring near the C-terminal of protein, even if they seem to be truncating loss-of-function mutations, may not be considered pathogenic, the mutations need to be variants on the 5’-terminal side rather than the variants established as

definitively pathogenic missense variants. Consideration shall be given to individually disclosing genes for which the management methods have been proposed in various guidelines.

(Note 9) For secondary findings useful for the health management of the patient's relatives, such findings shall be first communicated by the patient to their relatives, in principle, but it shall also be necessary for the medical staff to communicate such findings to the relatives depending on the patient's medical condition.

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Change log

1. First edition: Proposal concerning the process of information transmission in genomic medicine. Part 2: Specific principles of comprehensive germline genetic analysis using next-generation sequencing [First edition] (March 27, 2019)
   https://www.amed.go.jp/content/000045429.pdf

2. Revised edition: Proposal concerning the information transmission process in genomic medicine. Part 2: Specific principles of comprehensive germline genetic analysis using next-generation sequencing [Revised edition] (December 12, 2019)
   https://www.amed.go.jp/content/000056786.pdf

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Research Project on Ethical, Legal, and Social Issues Supported by the Health, Labour and Welfare Sciences Research Grants

"Extraction of ethical and social issues and improvement of social environment toward the realization of a society where people can benefit from genome medicine without anxiety"

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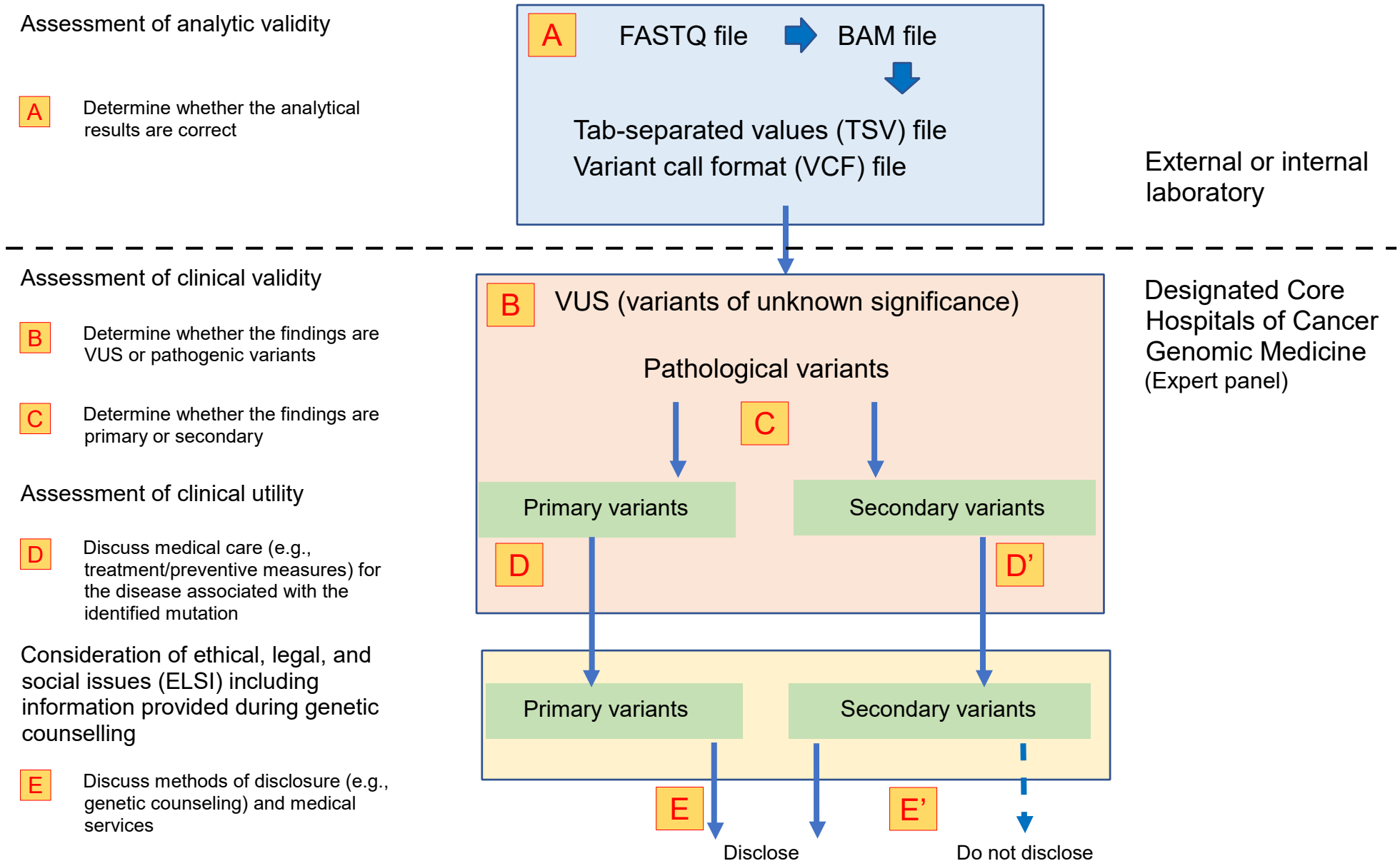
Appendix Figure 1. Flow for data obtained in the NGS panel



Comprehensive Tumor Genomic Profiling: Materials for Review of Secondary Findings, Ver. 1.0

August 16, 2021

Please ensure to use these materials by reference to “Proposal concerning the process of information transmission in genomic medicine. ― Part 1: Focusing on Comprehensive Tumor Genomic Profiling Analysis (Revised 2nd edition)” (https://www.amed.go.jp/news/seika/kenkyu/20200121.html). This proposal is currently under revision and will be released soon. (※)

Shinji Kosugi, Representative Researcher, Research Group for the Research Project on Ethical, Legal, and Social Issues Supported by the Health, Labour and Welfare Sciences Research Grants “Extraction of ethical and social issues and improvement of social environment toward the realization of a society where people can benefit from genome medicine without anxiety”

(※) Revision was releaed as “Guidelines for the Communication Process in Genomic Medicine Part 1: Focusing on Comprehensive Tumor Genomic Profiling”
(https://www.amed.go.jp/content/000087773.pdf)

Comprehensive Tumor Genomic Profiling: List of secondary findings to be disclosed to patients by the level of recommendation (Ver. 3.1_20210815)

Potentially Actionable SF Gene List			Panel	Level of recommendation for disclosure from the medical perspective (actionability) when pathological variants are confirmed in germline (Note 1)	Criteria for determining whether germline confirmatory testing should be performed when PGPV* is detected in the T-only Panel, and recommendation level (Note 2)
Gene	Major Phenotype	Remarks	F:FoundationOneCDx N:NCCOP		
APC	FAP		F/N	AAA	age<30
ATM	Cancer Predisposition Synd		F/N	A	◎
BAP1	BAP1 Tumor Predisposition Synd		F/N	B	Melanoma/Mesothelioma
BARD1	Cancer Predisposition Synd		F/N	B	◎
BMPR1A	Juvenile Polyposis			AAA	□
BRCA1	HBOC		F/N	AAA	◎
BRCA2	HBOC		F/N	AAA	◎
BRIP1	Cancer Predisposition Synd		F	A	◎
CDH1	HDGC		F	AA	○
CDK4	Melanoma		F/N	B	△
CDKN2A	Melanoma/Pancreatic Ca		F/N	A	△
CHEK2	Cancer Predisposition Synd		F/N	A	◎
EPCAM	Lynch	Deletion		AA	□
FH	Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)		F	B	Renal Cell Ca/Skin Ca/Soft tissue Sarcoma/Uterine Sarcoma
FLCN	Birt-Hogg-Dubé Syndrome (BHD)		F	B	Renal Cell Ca
HNF1A	MODY3	non-tumor	F	A	□
MAX	HPPS			AA	□
MEN1	MEN1		F/N	AAA	○
MET	Hereditary Papillary Renal Cancer (HPRC)		F/N	B	□
MLH1	Lynch		F/N	AAA	◎
MSH2	Lynch		F/N	AAA	◎
MSH6	Lynch		F/N	AAA	◎
MUTYH	MAP	Biallelic	F	AA	◎
NBN	Cancer Predisposition Synd		F	A	657del5 only
NF1	NF1		F/N	AA	age<30 & Breast Ca/Glioma/ Nerve Sheeth tumor/GIST/Pheochromocytoma
NF2	NF2		F/N	AA	△
PALB2	Cancer Predisposition Synd		F/N	AA	◎
PMS2	Lynch		F/N	AAA	◎
POLD1	Polymerase Proofreading-Associated Polyposis (PPAP)		F/N	A	□
POLE	Polymerase Proofreading-Associated Polyposis (PPAP)		F/N	A	Endometrial Ca/Glioma/Colon Ca
POT1	Malignant Melanoma			B	□
PTEN	PTEN Hamartoma		F/N	AAA	△
RAD51C	Cancer Predisposition Synd		F/N	A	◎
RAD51D	Cancer Predisposition Synd		F	A	◎
RB1	Retinoblastoma		F/N	AAA	age<30
RET	MEN2		F/N	AAA	◎
SDHA	HPPS		F	A	◎
SDHAF2	HPPS			AA	◎
SDHB	HPPS		F	AA	◎
SDHC	HPPS		F	AA	◎
SDHD	HPPS		F	AA	◎

SMAD3	Loeys-Dietz	non-tumor		A	□
SMAD4	Juvenile Polyposis		F/N	AAA	△
SMARCB1	Rhabdoid Tumor Predisposition Synd		F/N	B	△
STK11	Peutz-Jeghers		F/N	AAA	△
TERF2IP				B	□
TERT	Inherited Bone Marrow Failure Synd		F	B	□
TGFBR1	Loeys-Dietz	non-tumor		A	□
TGFBR2	Loeys-Dietz	non-tumor	F	A	△
TMEM127	Pheochromocytoma			AA	□
TP53	Li-Fraumeni		F/N	AAA	age<30 & Adrenocortical Ca/Bone Sarc/Breast Ca/Breast Sarc/Soft Tissue Sarc/Uterine Sarc
TSC1	Tuberous Sclerosis CompleX		F/N	AA	△
TSC2	Tuberous Sclerosis CompleX		F/N	AA	◎
VHL	VHL		F/N	AAA	◎(△Renal tumor)**
WT1	WT1-related Wilms		F	AA	□

Note 1	Level of recommendation for disclosure from the medical perspective (actionability) when pathological variants are confirmed in germline	
	Grade	Explanation
	AAA	Medical practice guidelines for pathological variant carriers are available in Japan
	AA	Hereditary tumor-causing genes in the ACMGSFv3 (73 genes)
		Genes listed in the NCCN guidelines recommended for disclosure consistently in major articles
	A	Genes listed in the NCCN guidelines recommended for disclosure inconsistently in major articles
		Other genes strongly recommended for disclosure consistently in major articles
		Causative genes other than hereditary tumor-causing genes in the ACMGSFv3 (73 genes)
	B	Genes recommended for disclosure only in some articles

Note 2	Criteria for determining whether germline confirmatory testing should be performed when PGPV* is detected in the T-only Panel, and recommendation level	
	Grade	Explanation
	◎	Confirmatory test should be performed, in principle, as the germline conversion rate is high
	○	Confirmatory test should be performed, if possible, as the germline conversion rate is somewhat high
	□	Confirmatory test should be performed, only in the presence of associated phenotypes, as data on the germline conversion rate is insufficient
	△	Confirmatory test should be performed, only in the presence of associated phenotypes, as the germline conversion rate is low
	Description of tumor name	Confirmatory test should be performed when the sample tumor (primary site) is described
	Description of age	Confirmatory test should be performed when the patient's age meets the described conditions
	Description of variant	Confirmatory test should be performed when the variant is consistent with a specific founder mutation
	**	In the case of renal tumor, confirmatory test should be performed in the presence of phenotypes of juvenile or other VHL disease

* Presumed Germline Pathogenic Variant refers to a pathological variant of a possible germline origin detected using T-only panel. If T-only panel is used, the decision shall be made regarding whether to disclose the findings based on the level of recommendation for disclosure as well as on the decision to perform a confirmatory germline test for the relevant PGPV.
Example 1) PGPV detected in TP53: Although the recommendation level was AAA, the patient was 65 years old and the tumor was not LFS-related; therefore, the expert panel determined that the significance of suggesting a confirmatory germline test is low and decided “not to disclose” the relevant PGPV.
Example 2) PGPV detected in RAD51D: The institution considered that findings with A-level recommendation should be disclosed. Based on the criteria for confirmatory germline testing for the relevant PGPV (◎), the expert panel decided to “disclose” the relevant PGPV so as to suggest a confirmatory test to the patient.
Example 3) PGPV detected in PTEN: Although the recommendation level was AAA, the grade was (△) on the criteria scale for confirmatory germline testing; therefore, phenotypic evaluation was requested through the genetic medicine section. As a result, the expert panel decided “not to disclose” the relevalnt PGPV because the phenotype of PTEN hamartoma syndrome was not found.

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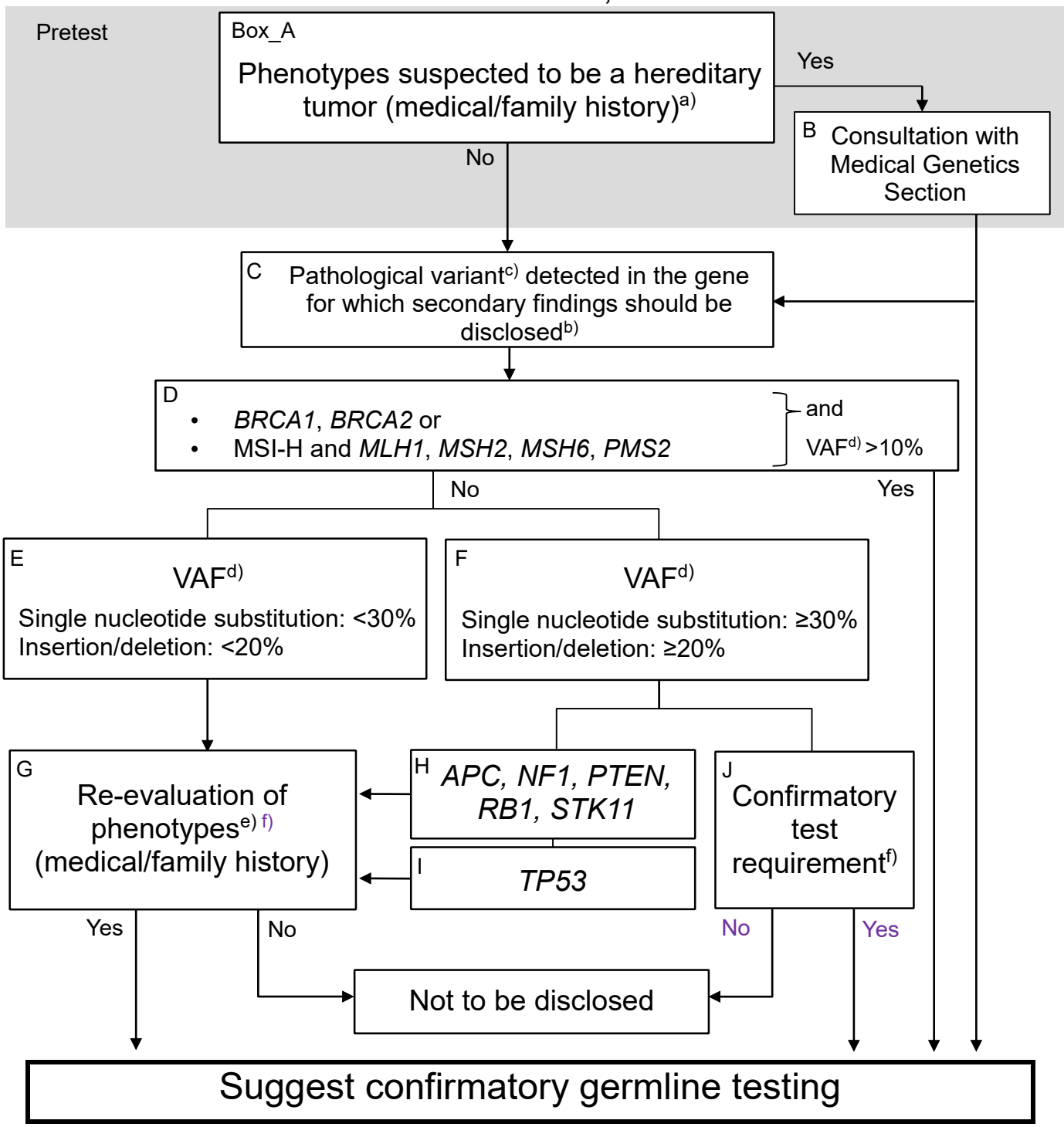
Operational guidelines for germline confirmatory testing of secondary findings in comprehensive tumor genomic profiling using tumor cells alone, Ver. 2



Refer to the guidance for details of each box.

a) Juvenile, multiple, familial, and other characteristic phenotypes (e.g., polyposis). Consult with the Medical Genetics Section if unknown.
b) Refer to the levels of recommendation for disclosure when detected in the germline.
c) Determine by reference to public databases (e.g., ClinVar and MGeND) and ACMG/AMP2015.
d) Variant Allele Frequency (with the cutoff criteria in accordance with the ESMO Guidelines 2019).
e) Evaluate hereditary tumor phenotypes corresponding to PGPV by reference to Gene Reviews Japan and Actionability Working Group-J.
f) Refer to the “Criteria for determining whether germline confirmatory testing should be performed.”

Operational guidelines for germline confirmatory testing of secondary findings in comprehensive tumor genomic profiling using tumor tissue alone, Ver. 2. Guidance dated 25/07/2021

1. Preface

The main objective of comprehensive tumor genomic profiling is to detect “druggable” somatic mutations specific to tumor cells, regardless of whether using tumor tissue cells alone or using tumor cells paired with normal peripheral blood cells. Therefore, even if pathological variants are suspected in the germline, tumor genomic profiling has a greater uncertainty in both detectability and specificity compared with dedicated genetic testing designed for the diagnosis of hereditary diseases.

These operational guidelines (hereinafter the “Operational Guidelines”) is intended for use in cases where the test result indicates a presumed germline pathogenic variant (PGPV), which is of germline origin, and may be clinically actionable, as a reference in determining whether the result should be disclosed and confirmatory testing should be recommended. Therefore, the Operational Guidelines shall not preclude medical institutions from developing their own standards in accordance with the actual circumstances of each institution conducting the test. Or rather, individual medical institutions need to have clear standards with reference to the Operational Guidelines.

It should be noted that even if the detected variant is determined not to be disclosed in light of the Operational Guidelines or original standards, it does not imply that it is ruled out as a pathological variant of germline origin.

2. Matters to consider before the test (Boxes A and B)

As a prerequisite for the Operational Guidelines, the phenotypes of the patient and his/her relatives need to be identified. In other words, the patient’s medical and family history, as well as physical and pathological findings, shall be reviewed for findings that may lead to a clinical diagnosis. If a hereditary disease is suspected based on the presence of phenotypes associated with a specific hereditary tumor, such as polyposis, in addition to the general characteristics of hereditary tumors (e.g., juvenile, multiple, and familial), a specialized clinical department or genetic medicine section at the same or another medical institution shall be requested to provide consultation separately from comprehensive tumor genomic profiling.

3. Genes for which secondary findings should be disclosed (Box C)

Even if a pathological variant is discovered in the germline, and identified as an actionable gene, whether it is actually actionable to provide surveillance or prophylactic treatment may vary from one medical institution to another. For this reason, the tests and subsequent actions to be taken shall be determined according to the actual situation at each medical institution by reference to the List of Secondary Findings in Comprehensive Tumor Genomic Profiling by the Level of Recommendation for Disclosure by Kosugi Group (2021) and the ACMG SF v3.0 73 genes.

4. Determination of pathological variants (Box C)

In selecting drugs based on the somatic variants, which is the main objective of comprehensive tumor genomic profiling, somatic mutation databases, such as COSMIC, are useful for evaluating pathogenicity. On the other hand, variants as secondary findings should be evaluated for pathogenicity in the germline. Therefore, decisions shall be made on the basis of the latest evidence with reference to ACMG/AMP2015 while referring to the data on the germline in public databases, such as ClinVar and MGeND.

This flow shall apply to nucleotide substitutions and small insertions/deletions in coding regions and splicing boundaries detected by comprehensive tumor genomic profiling. In addition, copy number variations (CNVs), such as loss, and amplification can also be detected by comprehensive tumor genomic profiling but shall not be included in this flow for the moment (see "6. Variant allele frequency"). If a germline confirmatory test for loss is feasible at the medical institution, disclosure shall be considered based on the level of recommendation.

5. Specific genes for which germline testing is recommended regardless of allele frequency (Box D)

Two genes, *BRCA1* and *BRCA2*, correspond to the genes with a low variant allele frequency (VAF) but with a high probability of germline origin. If immunohistochemical staining shows dMMR or microsatellite instability (MSI) and pathological variants in mismatch repair genes, confirmatory germline testing shall be suggested considering potential Lynch syndrome. Even if no MSI is observed, the possibility that the pathological variant in the MMR gene is of germline origin may not be ruled out, so in the case of MSS, proceed to Boxes E and F to reevaluate the variant.

One of the reasons for treating these genes separately from other genes is that diseases that originated from these genes (hereditary breast and ovarian cancer syndrome, Lynch syndrome) have a substantial body of evidence for the medical management and surveillance of pathological variant carriers. It is advisable for each medical institution to have a management system in place for these pathological variant carriers.

6. Variant allele frequency (VAF) (Boxes E and F)

VAF information can be used to evaluate whether variants such as single nucleotide substitutions and small deletions/insertions are of germline origin but cannot be evaluated because no VAF information is available for CNV.

If the tumor cell percentage (purity assessment) of the sequence specimen is high, even pathological variants of somatic cell origin may show a high VAF apparently due to loss of the wild-type allele or amplification of the variant allele. In particular, tumor suppressor genes, even those of somatic cell origin, may show values up to the same level as the tumor cell percentage. On the other hand, if the tumor cell percentage is low, variants shall be suspected to be of germline origin regardless of the value if the VAF significantly exceeds the tumor cell percentage.

7. Phenotype re-evaluation (Box G)

After confirming that evaluable clinical information (see 2) has been obtained, phenotypes shall be re-evaluated based on the variant information with reference to GeneReviewsJapan, Actionability Working Group-J. In this case, the evaluation should be more disease-specific than that in Box A; therefore, it is advisable to evaluate the phenotypes in cooperation with a clinical geneticist and relevant departments.

It should be noted that the phenotypic re-evaluation in this Box shall be conducted in the flow from Box E and in the flows from Boxes H and I, but these flows have different implications. The flow from Box E is intended to avoid overlooking specific hereditary tumor phenotypes suspected on the basis of PGPV considering the fact that some variants of germline origin show a low VAF. On the other hand, the flows from Boxes H and I are intended to confirm the absence of the relevant hereditary tumor phenotype for genes frequently found in tumor cells, but are infrequently of germline origin, and show relatively clear phenotypes if they are of germline origin.

8. Genes recommended for phenotypic evaluation in case of high VAF (Box H)

The group of genes presented in this box, of which pathological variants are frequently detected in tumor cells, is likely to have some phenotype if they are of germline origin. Therefore, if a PGPV is detected in these genes, a germline test shall be suggested as necessary after evaluating the corresponding hereditary disease by a specialist.

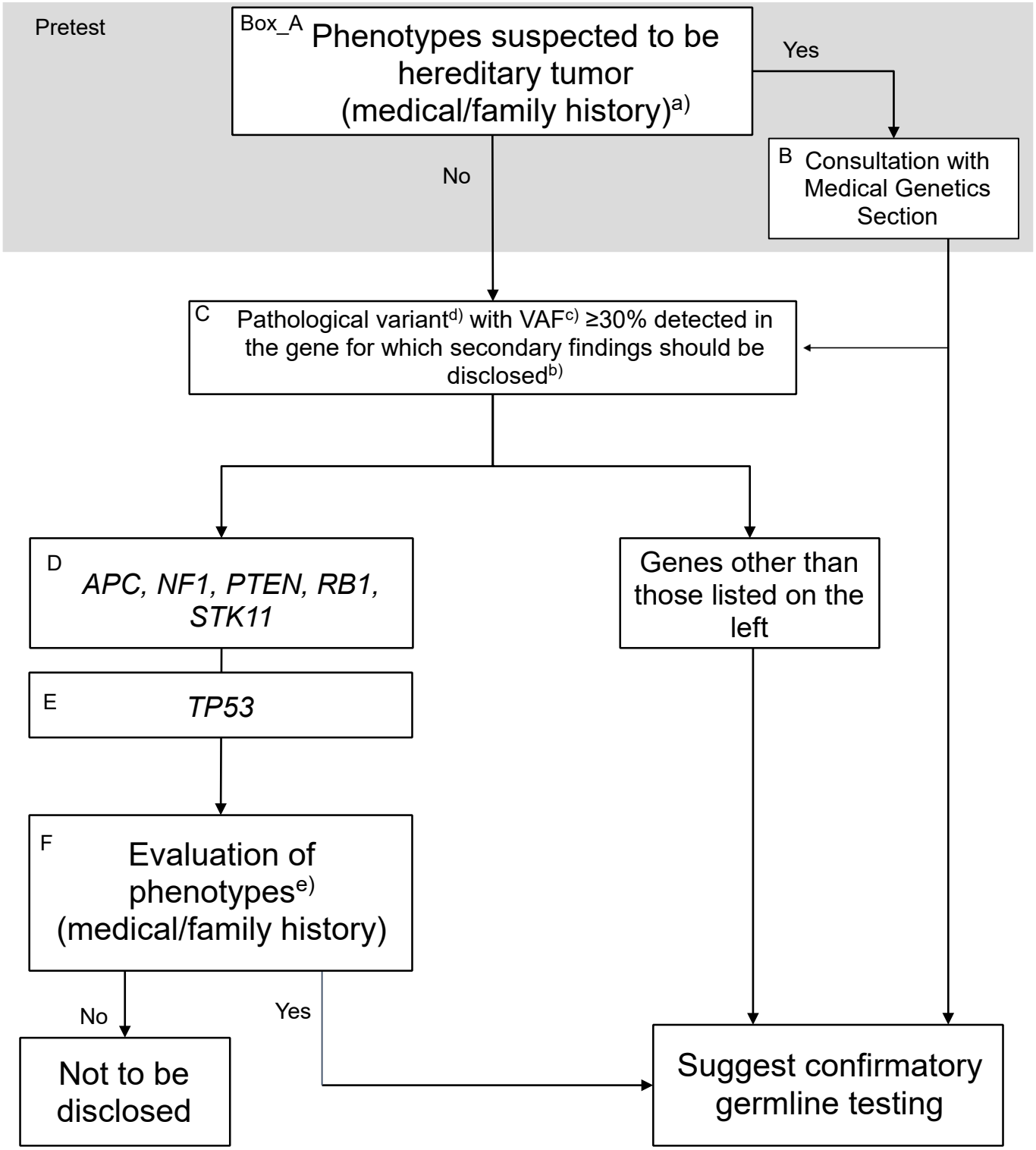
9. *TP53* gene (Box I)

Pathological variants are frequently detected, most of which are suggested to be of somatic cell origin. On the other hand, pathological variants of *TP53* have recently been reported to have a high general population frequency, and multi-gene panel genetic testing has identified cases with no clear phenotype that do not meet the revised Chompret criteria (2015), which are considered highly sensitive. It is also advisable to refer to phenotypes other than medical history and family history, such as cancer types with frequent pathological variants in the somatic cells of *TP53*, including tissue subtypes.

10. Necessity of confirmatory testing (Box J)

The necessity of confirmatory testing shall be evaluated with reference to the “Criteria for determining whether germline confirmatory testing should be performed when PGPV is detected in the T-only Panel (Note 2)” in the “Comprehensive Tumor Genomic Profiling: List of secondary findings to be disclosed to patients by the level of recommendation.” In principle, it is required to conduct a germline confirmatory testing for PGPVs with a high VAF leading to Box J regardless of the presence or absence of the phenotype of the associated hereditary tumor, but the necessity of confirmatory testing shall be evaluated for some genes considering the fact that the frequency of variants of germline origin is low except for certain phenotypes.

Operational guidelines for germline confirmatory testing of secondary findings in comprehensive tumor genomic profiling (liquid biopsy) using circulating tumor DNA in blood, Ver. 1



Refer to the guidance for details of each box.

a) Juvenile, multiple, familial, and other characteristic phenotypes (e.g., polyposis). Consult with clinical geneticists if unknown.

b) Refer to the levels of recommendation for disclosure when detected in the germline.

c) Variant Allele Frequency

d) Determine by reference to public databases (e.g., ClinVar and MGeND) and ACMG/AMP2015.

e) Evaluate hereditary tumor phenotypes corresponding to PGPV by reference to Gene Reviews Japan and Actionability Working Group-J.

Operational guidelines for germline confirmatory testing of secondary findings in comprehensive tumor genomic profiling (liquid biopsy) using circulating tumor DNA in blood, Ver. 1. Guidance dated 25/07/2021

1. Preface

The main objective of comprehensive tumor genomic profiling for circulating tumor DNA in blood is to detect “druggable” somatic mutations specific to tumor cells. Therefore, although blood tests are employed, they are intended to analyze tumor DNA, and even if pathological variants are suspected in the germline, tumor genomic profiling has a greater uncertainty in both detectability and specificity compared with dedicated genetic testing designed for the diagnosis of hereditary diseases.

These operational guidelines (hereinafter the “Operational Guidelines”) is intended for use in cases where the test result indicates a presumed germline pathogenic variant (PGPV), which is of germline origin, and may be clinically actionable, as a reference in determining whether the result should be disclosed and confirmatory testing should be recommended. Therefore, the Operational Guidelines shall not preclude medical institutions from developing their own standards in accordance with the actual circumstances of each institution conducting the test. Individual medical institutions need to have clear standards for disclosure with reference to the Operational Guidelines.

It should be noted that even if the detected variant is determined not to be disclosed in light of the Operational Guidelines or original standards, it does not imply that it is ruled out as a pathological variant of germline origin.

2. Matters to consider before the test (Boxes A and B)

As a prerequisite for the Operational Guidelines, the phenotypes of the patient and his/her relatives need to be identified. In other words, the patient’s medical and family history, as well as physical and pathological findings, shall be reviewed for findings that may lead to a clinical diagnosis of hereditary tumor. If a hereditary disease is suspected based on the presence of phenotypes associated with a specific hereditary tumor, such as polyposis, in addition to the general characteristics of hereditary tumors (e.g., juvenile, multiple, and familial), a specialized clinical department or genetic medicine section at the same or another medical institution shall be requested to provide consultation separately from comprehensive tumor genomic profiling.

3. Genes for which secondary findings should be disclosed (Box C)

Even if a pathological variant is identified as an actionable gene, whether it is actually actionable may vary from one medical institution to another. For this reason, the tests and subsequent actions to be taken shall be determined according to the actual situation at each medical institution by reference to the List of Secondary Findings in Comprehensive Tumor Genomic Profiling by the Level of Recommendation for Disclosure by Kosugi Group (2021) and the ACMG SF v3.0 73 genes.

4. Determination of pathological variants (Box C)

In selecting drugs based on the somatic variants, which is the main objective of comprehensive tumor genomic profiling, somatic mutation databases, such as COSMIC, are useful for evaluating pathogenicity. On the other hand, variants as secondary findings should be evaluated for pathogenicity in the germline. Therefore, decisions shall be made on the basis of the latest evidence with reference to ACMG/AMP2015 while referring to the data on the germline in public databases, such as ClinVar and MGeND.

This flow shall apply to nucleotide substitutions and small insertions/deletions in coding regions and splicing boundaries detected by comprehensive tumor genomic profiling. In addition, copy number variations (CNVs), such as loss, and amplification can also be detected by comprehensive tumor genomic profiling but shall not be included in this flow as they are not currently covered by public health insurance.

5. Genes recommended for phenotypic evaluation in case of high VAF (Box D)

The group of genes presented in this box, of which pathological variants are frequently detected in tumor cells, is likely to have some phenotype if they are of germline origin. Therefore, if a PGPV is detected in these genes, a germline test shall be suggested as necessary after evaluating the corresponding hereditary disease by a specialist.

6. *TP53* gene (Box E)

Pathological variants are frequently detected, most of which are suggested to be of somatic cell origin. On the other hand, pathological variants of *TP53* have recently been reported to have a high general population frequency, and multi-gene panel genetic testing has identified cases with no clear phenotype that do not meet the revised Chompret criteria (2015), which are considered highly sensitive. It is also advisable to refer to phenotypes other than medical history and family history, such as cancer types with frequent pathological variants in the somatic cells of TP53, including tissue subtypes.

7. Phenotype evaluation (Box F)

After confirming that evaluable clinical information (see 2) has been obtained, phenotypes shall be re-evaluated based on the variant information with reference to GeneReviewsJapan, Actionability Working Group-J. In this case, the evaluation should be more disease-specific than that in Box A; therefore, it is advisable to evaluate the phenotypes in cooperation with a clinical geneticist and relevant departments.