Proposal concerning the information transmission process in genomic medicine

Part 1: Focusing on comprehensive tumor genomic profiling analysis

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1. Introduction

The marked increase in speed of genome/gene analysis using next-generation sequencing technology has made it possible to analyze many or all genes at a time, and this technology has begun to be applied to daily clinical practice. The Guidelines for Genetic Tests and Diagnoses in Medical Practice by the Japanese Association of Medical Sciences (2011)[1)] provide the basis for genetic testing, and they require novel ideas and systems from the viewpoint of multigene or comprehensive gene analysis, in addition to ideas and systems used for conventional analysis of a small number of target genes.

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

Moreover, new effective drugs, such as molecularly targeted drugs and enzyme replacement therapy, are becoming available, but exact determination of the condition of the genes of the target molecule is often required. Progress of such genomic/gene analysis technology and therapeutic drugs is an asset shared by the entire human race. It is our urgent task to realize medical care using genomic information that appropriately includes genomic medicine, and as many people as possible, including patients and their families, must benefit from it.

2. Objective

This proposal aims to urge medical workers to transmit information concerning genomic medicine through appropriate processes to allow patients and their families to sufficiently understand genomic medicine, and to have the disclosed genomic information be properly applied to medical care and health management of patients and their families. All persons and organizations, including related scientific societies, are expected to retain a high level of morality, and to respect and properly respond to this proposal in order for genomic medicine to become useful by gaining the understanding and trust of patients, families, and society.

3. Targets of this proposal

The targets of this proposal are tests for multiple simultaneous or comprehensive gene analysis using next-generation sequencing performed as clinical tests in medical practice. Presently, the following 2 procedures, whose clinical application is progressing, are specific targets, but new targets may be added in the future.

I) So-called tumor profiling (comprehensive tumor genomic profiling; CGP) analysis performed for detecting somatic mutations in cancer cells for the diagnosis, treatment, and prognosis of cancer. (In tumor profiling analysis, only tumor tissue is examined, or variants in the tumor tissue and germline are tested simultaneously (using normal cells or blood samples). In the former case, if the mutations is suspected to be germline origin, it should be confirmed. The flows concerning secondary findings in such tests are summarized in Accompanying Table 1.

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

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

In germline gene analyses performed as research, even if the results are disclosed to patients, this proposal, targeted to medical care exclusively for the diagnosis or treatment, is not applied because the analytical precision, measures to assess it, procedure for disclosure, and cost are considered to vary widely among studies. However, this proposal may also be referred to in disclosure of the results obtained through research. In addition, compliance with the Japanese ethical guidelines for human genome/gene analysis research[2)] is required.

4. Basic attitude

Characteristics of genetic information of the germline are clearly stated in the Guidelines for Genetic Tests and Diagnoses in Medical Practice by the Japanese Association of Medical Sciences (2011).[1)] Among them, particular attention is necessary concerning the following points: They do not change over the lifetime, they are partly shared among relatives, there are times when genotypes and phenotypes of related individuals can be predicted with a relatively precise probability or when the development of a disease can be predicted almost certainly before the onset, and the information may cause social disadvantages to the patients and their relatives if it is utilized inappropriately.

The analytical results obtained by next-generation sequencing include “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 explain the main objective of the test in detail, it is also necessary to make sure to explain the possibility of detection of secondary findings and gain understanding in advance.

5. Definition of secondary findings (Note 1)

Conventionally, the term “incidental findings/secondary findings” was often used, but this proposal proposes to separately refer to clear pathogenic variants as “primary findings” if they are the original targets of the test and “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 this proposal.

In I), detection of variants confirmed to be pathogenic in the germline

In II), detection of variants confirmed to be pathogenic that cause symptoms other than those targeted to be diagnosed

Here, variants confirmed to be pathogenic mean mutations targeted by the tests with “analytical validity” and “clinical validity” established by the Guidelines for Genetic Tests and Diagnoses in Medical Practice by the Japanese Association of Medical Sciences (2011),[1)] and specifically, truncating loss-of-function mutations or authentic variants registered as pathogenic in ClinVar or public databases, in principle. However, as there is the possibility that even information registered in public databases may be false positive, information, including clinical information, must be evaluated by an expert panel in an integrated manner (See 6.(3) below).

6. Specific principles of tumor profiling analysis

(1) Points of attention in pretest explanation

① Pretest explanation for tumor profiling analysis must be conducted primarily by physicians in charge, such as experts in cancer chemotherapy, in compliance with the following points of attention. In addition, to deepen the understanding of patients and their families based on sufficient explanation, it is desirable to appoint staff members who give supplementary explanation and to prepare a system to gain support.

② If patients and their families are given an explanation about cancer and its treatment, they are often barely able to understand the explanation. Therefore, sufficient consideration must be given to the timing of explanation of tumor profiling analysis.

③ Tests are performed primarily for cancer treatment, and a detailed pretest explanation must be given chiefly by an attending physician with sufficient experience in necessary treatments (cancer chemotherapy, surgery, and radiotherapy, etc.) or a specialist physician by taking sufficient time. The physician who gives the explanation must also properly explain germline mutations (synonymous to secondary findings in tumor profiling analysis). It is desirable that the physician who gives the explanation is also appropriately informed and trained concerning secondary findings.

④ As there is the possibility of detecting secondary findings, it is desirable that the pretest explanation also be given to accompanying family members such as the patient’s spouse or children. (This is also desirable from the viewpoint of cancer treatment. However, the presence of attendants is not essential if there is a time constraint for cancer treatment. Moreover, the wishes of the patient must be respected concerning the presence of attendants.)

⑤ However, pretest explanation concerning secondary findings must be made in consideration of its balance with the explanation of the original objective of the tests. (The original objective of the tests is cancer treatment, and overemphasis of the explanation of secondary findings is preposterous.)

⑥ After the patient has sufficiently understood the explanation, whether the patient wishes disclosure if secondary findings for which there are coping methods, such as treatments/preventive measures are considered useful for the health management of the patients/relatives, must be confirmed before the analysis, in principle (Note 2), and the wishes must be written on the consent form. However, it must also be explained that the patient has the right to remain uninformed based on sufficient understanding.

⑦ In anticipation of situations in which it becomes difficult to directly inform the patient of the results, such as a sudden change in the condition or death, it is recommended to prepare a consent form or a space on the form in which the names and contact information of family members (surrogates) to whom the analytical results can be disclosed if secondary findings are useful for the health management of relatives. (It is desirable that "family members (surrogates)" whose names and contact information are indicated in the consent form are present at interviews, such as the one for pretest explanation, are informed of the disease condition of the patient and tumor profiling analysis in advance, and are able to confirm the will about disclosure. This space may be left in blank or be filled in later.)

⑧ It is desirable that the patient's interests, questions, and worries be responded to first by the medical staff involved in cancer treatment, and that a system be established for requesting support from specialists in clinical genetics (clinical geneticists) and certified genetic counselors from the time of pretest explanation depending on the state of anxiety, if necessary (many family histories of cancer, vague anxiety over "cancer family").

⑨ It is necessary that a system to respond to the needs for genetic counseling that patients and their relatives may develop associated with findings related to germline mutations (establishment of a division for clinical genetics, system for referral) be prepared.

⑩ Informed consent must be received from patients after they and their families have sufficiently understood the above contents.

⑪ In tumor profiling testing using tumor tissue alone, it is necessary to explain in advance that if germline mutations for which there are coping methods, including treatments and preventive methods considered useful for the health management of the patients and their relatives, are suspected, additional examinations to confirm them will be necessary, and consent must be received as to whether they wish to be informed of such secondary findings that are suspected.

⑫ If the patient, such as a child, is judged to lack the ability to consent, the explanation is given

to and consent is received from an appropriate surrogate,, but it is desirable to receive informed assent according to the patient's ability to understand .

(2) Contents of pretest explanation

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

② The primary 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 There is the possibility that the analysis itself ends in failure depending on the quality or quantity of the samples analyzed.

⑦ Approximate results currently obtained concerning ③-⑥ above are shown.

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 core and cooperation hospitals of cancer genomic medicine certified by 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 tumor profiling analysis) can be detected with a certain probability (Note 4).[3)4)5)] However, not all secondary findings can be detected.

⑪ There may or may not be coping measures (treatments and preventive methods) for the expected phenotypes (some are not those of cancer) depending on secondary findings.

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

⑬ If secondary findings which are medically actionable, such as treatments/preventive measures considered useful for the health management of the patients/relatives (e.g., genes responsible for hereditary tumors), are detected, the information can be used proactively. Not using such information may lead to disadvantages. However, the patients/relatives have the right to remain uninformed about it with sufficient understanding. Moreover, it is possible to make or change this decisions at an appropriate timing.

⑭ It is difficult to disclose secondary findings for which there are no coping methods or coping methods are unclear. (By analyses using next-generation sequencing, an immense amount

of data is automatically generated, and it is necessary to select data relevant to the objective of the test (primary findings) and evaluate their accuracy. Although an immense amount of data unrelated to the primary objective of analysis is also generated, it is practically impossible to evaluate all of them (accuracy of the data and probability of pathogenicity)).

⑮ As a large amount of data obtained by tumor profiling analysis, including both primary and secondary findings, are accumulated and expected to aid in the future development of medicine and welfare of patients, it is desirable that the data be shared with strict management of personal information.

⑯ In tumor profiling testing using tumor tissue alone, if germline mutations for which there are coping methods, such as treatments/preventive measures considered useful for the health management of the patients/relatives, are suspected, additional tests for confirmation are necessary. However, the information that there are choices not being informed of the possibility of secondary findings and not perusing confirmation testing should be informed to patients.

(3) Evaluation of the test results

① To evaluate the individual results of tumor profiling analysis in an integrated manner, multidisciplinary conferences participated in by the attending physician, experts in cancer chemotherapy, pathologists, clinical geneticists and certified genetic counselors specializing in genetic medicine and genetic counseling, bioinformaticians, experts knowledgeable about molecular genetics and cancer genomic medicine, and pharmacists, nurses, clinical technicians, and clinical research coordinators (CRC) engaged in the diagnosis and treatment of cancer (expert panel) must be held regularly (Note 5).

② In the expert panel, the following points must be evaluated, in principle: (A) Judgment about the analytical validity of the test results (this item may not be included if the tests are commissioned by an outside organization), (B) judgment of whether the finding is a VUS (variant of uncertain significance) or pathogenic variant, (C) judgment of whether the finding corresponds to a primary or secondary finding (judgment of clinical validity by combining (B) and (C)), (D) judgment of clinical usefulness (evaluation of medical actions such as therapeutic and preventive measures for the diseases related to the identified pathogenic variants including primary and secondary findings), and (E) consideration of ethical, legal, and social viewpoints (methods for disclosure of the results, methods for providing medical care) (See Figure 1, Attached Table 2).

③ The expert panel must evaluate the content and points of attention of treatment. Concerning the off-label use of drugs and drugs not approved in Japan, it evaluates provision of information concerning clinical studies and treatments under appropriate systems, such as clinical trials, advanced medical treatment, and patient-requested treatment, and measures

to take if multiple drugs become candidates in addition to how the patients (surrogates in some cases) should be informed of the test results (primary findings).

④ Concerning the items of tumor profiling analysis reports, classification according to the evidence level, and selection of treatment to be evaluated by the expert panel, reports including the Clinical Practice Guidance for Next-generation Sequencing in Cancer Diagnosis and Treatment by the Japanese Society of Medical Oncology, Japan Society of Clinical Oncology, and the Japanese Cancer Association (Note 6)[6)7)8)], should be referred to.

⑤ Although the primary task of the expert panel is to evaluate primary findings, regarding secondary findings, it must also sufficiently discuss whether there are matters to be disclosed such as those shown in (4) below, whether tests for confirmation are necessary, what are specific advantages associated with disclosure, and points of attention and methods for disclosure while paying attention to different aspects of each gene. If necessary, experts in the department that treats the disease related to the secondary findings and those in other facilities should also participate in the discussion.

⑥ If tumor profiling testing using tumor tissue alone has yielded results suspected to be secondary findings to be disclosed and if tests of germline mutations for confirmation are necessary (Note 7), a system for implementing the tests or commissioning them to an outside organization must be established.

⑦ If tests of germline mutations for confirmation are necessary, it is desirable to evaluate measures to minimize the financial burden of the patient such as its inclusion in the initial cost (Note 8).

(4) Secondary findings to be disclosed

① Variants highly likely to be pathogenic for which there are clinically established treatments/preventive measures that are useful for the health management of the patients/relatives

② Specifically, truncating loss-of-function mutations or unquestionably pathogenic variants registered as “pathogenic” alone in public databases such as ClinVar or (Note 9)

③ Findings should not be disclosed if they are not sufficiently accurate or reliable, and may thus pose a psychological burden to patients/relatives or invite misunderstanding, and are not clearly more beneficial than harmful.

④ Genes to be disclosed should be evaluated by referring to the 59 genes specified by the ACMG (American College of Medical Genetics and Genomics) recommendations,[9)] the disclosure of which is recommended based on the severity of their effects on life and the possibility of treatment/prevention (Note 9).

⑤ The findings used for the diagnosis of asymptomatic carriers should not be disclosed, in

principle, because they are not presently considered directly beneficial to the health management of the patients/relatives.

(5) Points of attention in disclosure of secondary findings

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

② If the patient wishes disclosure in advance, and if no secondary findings to be disclosed are detected or if no secondary findings to be disclosed are suspected by tumor profiling analysis using tumor tissue alone, the attending physician must inform this while explaining the results concerning primary findings. It must be noted that no detection or suspicion of secondary findings to be disclosed does not mean the absence of secondary findings. Furthermore, if secondary findings to be disclosed are suspected on tumor profiling analysis using tumor tissue alone, tests for confirmation of secondary findings must be performed by obtaining informed consent again.

③ When the secondary findings to be disclosed have been determined, they must be disclosed in an environment that ensures protection of privacy by an organization with an appropriate staff, including a specialist in clinical genetics (clinical geneticist) and certified genetic counselor capable of providing sufficient genetic counseling.

④ Cooperation with departments and experts related to the secondary findings in and out of the facility must be implemented.

⑤ The timing of disclosure of secondary findings may not necessarily be simultaneous with disclosure of primary findings and should be decided in an integrated manner, in consideration of 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 In this situation, it is desirable to evaluate minimization of the additional cost for the patient to receive genetic counseling at each facility (Note 8).

⑦ Depending on the circumstances, it is necessary to contact the “family member (surrogate) to whom the analytical results may be disclosed if 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 finding to be disclosed to the “family (surrogate)” must be the same as the secondary findings to be disclosed to the patient, in principle.).

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

① For patients in whom secondary findings have been confirmed and their relatives, continuous genetic counseling should be conducted at an appropriate timing to link them to periodical surveillance without omission and sharing of information among a wider range of relatives.

② A system to implement germline genetic testing to examine whether relatives have the same

variant must be established.

③ Continuous support must be offered to patients/families such as by informing them of the psychological support system (clinical psychologists, palliative care team) set up in the consultation and support center and medical organizations.

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

Basically following the same line of thought as “6. Specific principles of tumor profiling analysis”, irrelevant items may simply be deleted. However, whole exome or whole genome sequencing performed for intractable diseases has characteristics different from tumor profiling analysis such as that the pathogenic significance of detected gene variants is unclear in relatively many cases and that secondary findings may be related to a wide range of diseases. In many cases, it is necessary to make elaborate preparations before disclosure of the results. In addition to sufficient genetic counseling, it is necessary to provide or refer the patients to new medical care if secondary findings requested to be disclosed have been detected, and it will be necessary to separately collect their costs. Therefore, another proposal will be made concerning comprehensive genetic testing of intractable diseases (Note 12).

8. Preparation of conditions to make more satisfactory coping with secondary findings possible

Fulfillment of conditions such as

① Tests for confirmation of germline mutations for which there are treatments/preventive methods, such as those of the ACMG59 genes[9], can be performed as part of medical practice (i.e., there is a facility that can perform the tests, and the tests can be performed at a reasonable cost by means of health insurance and benefit for advanced medical services).

② Such tests are reasonably accurate.

③ Population-specific databases that facilitate accurate judgments of the pathologenic significance of detected variants are developed further.

④ The system for genetic counseling is improved.

is a prerequisite and a theme to be evaluated separately from this proposal.

9. Other points

Matters not mentioned in this proposal should 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 this proposal proposes to separately refer to clearly pathogenic variants as “primary findings” if they are original targets of the tests and “secondary findings” if they are related to genes other than the original targets because the term “incidental findings” may attenuate the awareness that the findings are targets of analysis and a delay of response if they have occurred. This definition of “secondary findings” slightly differs from the definition in the report by the Presidential Commission for the Study of Bioethical Issues[10] or by the ACMG.[5] 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” and mentions “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[11] require separate assessment of 24 diseases (presently 59 genes related to 27 diseases[9]) 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 that have 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 because it is still premature to define the ACMG59 genes[9] as actionable and because the actionability varies under different situations. “Secondary findings” defined here include those that have treatments/preventive measures and should be disclosed and those without treatments/preventive measures. After accepting these conditions, it is necessary for the expert panel to carefully evaluate 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 necessary to pay attention to the fact that the definition of hereditary tumor as a secondary finding on tumor profiling analysis is becoming vague. However, as consistently using the expression “pathogenic germline variants detected by tumor profiling analysis” is inconvenient, we propose them to be termed “secondary findings” to facilitate communication among core and cooperation hospitals of cancer genomic medicine throughout Japan.

(Note 2) Concerning requests for disclosure of secondary findings, the wishes are heard before the tests and confirmed before disclosure, in principle, but a procedure in which the wishes are confirmed by the time of disclosure without requiring final decision-making before implementation of the tumor profiling analysis may be considered. In addition, it is necessary to remind the patients that they have the right to retract consent. If a germline mutation is suspected by tumor profiling

analysis using tumor tissue alone, thus requiring a test for confirmation, it is necessary to reconfirm the patient's wishes about implementation of a test for confirmation at an appropriate time such as the time of disclosure of primary findings. In this case, it is desirable for a specialist in clinical genetics or a certified genetic counselor to cooperate in the explanation to the patient.

(Note 3) An explanation including information concerning the current cancer medication (information concerning drugs covered by health insurance and state of clinical trials of drugs not approved in Japan) is necessary.

(Note 4) In general, when tumor profiling analysis is performed, germline mutations are reportedly detected at a rate of a few percent,[3)4)5)] but the frequency of detection of germline mutations 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 Ashkenazic Jews,[12)13)] and there is the possibility of identification of germline mutations latently present in such cancers by tumor profiling analysis.

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

(Note 6) This proposal focuses on the process of transmitting information in genomic medicine, and Clinical Practice Guidance for Next-generation Sequencing in Cancer Diagnosis and Treatment by the Japanese Society of Medical Oncology, Japan Society of Clinical Oncology, and the Japanese Cancer Association[6)] should be referred to for the entire diagnosis and treatment for cancer based on tumor profiling analysis.

(Note 7) In tumor profiling analysis, variants are investigated in tumor tissue alone or simultaneously in the tumor tissue and germline (using normal cells and blood samples). In the former, the possibility of germline mutations is evaluated in an integrated manner according to information, including the gene name, variants in agreement with the germline founder mutations, age at the onset, history of present illness, clinical history, familial history, allele frequency, and percentage of tumor cells.[14)] Figure 2 may be consulted for this judgment. If germline mutations are suspected, tests to confirm them are necessary. However, if simultaneous analysis with sufficient quality control has been carried out, no retest is necessary, in principle. However, tests for confirmation are necessary without sufficient quality control of the analysis.

(Note 8) There are methods to reduce the cost such as inclusion of the fees for genetic counseling necessary for disclosure of secondary findings in the initial cost of testing. However, the necessary cost may be charged if relatives receive separate genetic counseling following the patient or undergo genetic tests (6.(6)①②).

(Note 9) The handling of likely pathogenic variants must be evaluated carefully by the expert panel. The ACMG guidelines[15] should also be referred for the evaluation of variants. In addition, as nonsense variants/frameshift variants occurring near the C-terminal of protein, even if they seem to be truncating loss-of-function mutations, may not be considered pathogenic, although rarely, it is necessary that the variants are those of the 5'-terminal side rather than a variant established as a definitively pathogenic missense variant. Disclosure concerning genes for which for the management methods have been proposed by different guidelines must be evaluated individually.

(Note 10) Concerning disclosure of secondary findings useful for health management of relatives, they are transmitted from the patient to the relatives, in principle, but it may be necessary for the medical staff to transmit them to the relatives depending on the patient's condition. In such a situation, whether the family (surrogate) should be contacted by the attending physician of the relevant department or the genetic counseling division must be judged individually in consideration of the relationship between the medical staff and the patient or family (surrogate), and the necessity of explaining the patient's condition.

(Note 11) This proposal is not directly targeted to germline multi-gene panel analysis of disease groups (usually analyzing several tens to several hundreds of genes) because it is theoretically considered to yield no secondary findings. However, as there is the possibility of detection of mutations in initially unexpected genes in gene panels that include a large number of genes, the principles of this proposal may be used as a reference.

(Note 12) See "Proposal concerning the process of information transmission in genomic medicine. Part 2: Specific principles in comprehensive genetic testing of germline using next-generation sequencing".

References

1） Guidelines for Genetic Tests and Diagnoses in Medical Practice. The Japanese Association of Medical Sciences (2011) http://jams.med.or.jp/guideline/genetics-diagnosis.pdf

2） “Japanese ethical guidelines for human genome / gene analysis research” Ministry of Education, Culture, Sports, Sciences and Technology, Ministry of Health, Labour and Welfare, Ministry of Economy, Trade and Industry (partly modified in 2017) http://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000153405.pdf

3） Meric-Bernstam F, Brusco L, Daniels M et al. Incidental germline variants in 1000 advanced cancers on a prospective somatic genomic profiling protocol. Ann Oncol 2016; 27: 795–800.

4） Kou T, Kanai M, Yamamoto Y, et al. Clinical sequencing using a next-generation sequencing-based multiplex gene assay in patients with advanced solid tumors. Cancer Sci. 2017;108:1440-1446.

5） Schrader KA, Cheng DT, Joseph V et al. Germline Variants in Targeted Tumor Sequencing Using Matched Normal DNA. JAMA Oncol. 2016; 2:104-11.

6） Collaborative work of the Japanese Society of Medical Oncology, Japan Society of Clinical Oncology, and the Japanese Cancer Association. Clinical practice guidance for next-generation sequencing in cancer diagnosis and treatment (October 11, 2017) http://www.jca.gr.jp/researcher/topics/2017/files/20171013.pdf

7） Appendix 1 of the reference 6: Evidence level-based classification http://www.jca.gr.jp/researcher/topics/2017/files/20171013_guidance_1.pdf

8） Appendix 2 of the reference 6: Evidence level http://www.jca.gr.jp/researcher/topics/2017/files/20171013_guidance_2.pdf

9） Sarah S. Kalia ScM, Adelman K, et al.: Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. 2016, Genet Med advance online publication, November 17, doi:10.1038/gim.2016.190

１０） ANTICIPATE and COMMUNICATE Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts. Presidential Commission for the Study of Bioethical Issues. Dec 2013 http://bioethics.gov/sites/default/files/FINALAnticipateCommunicate_PCSBI_0.pdf

１１） ACMG Board of Directors.: ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing Genet Med 17: 68-69, 2014.

１２） Hirasawa A, Imoto I, Naruto T, et al.: Prevalence of pathogenic germline variants detected by multigene sequencing in unselected Japanese patients with ovarian cancer. Oncotarget 2017; ;

8(68):112258-112267.

１３） Modan B, Hartge P, Hirsh-Yechezkel G, et al. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. N Engl J Med 2001; 345: 235–240.

１４） Li MM, Datto M, Duncavage EJ, Kulkarni S, Lindeman NI, Roy S, Tsimberidou AM, Vnencak-Jones CL, Wolff DJ, Younes A, Nikiforova MN. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn. 19:4-23. 2017

１５） Richards S, Aziz N, Bale S, et al. on behalf of the ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 17:405–423, 2015

AMED Program for Promoting Platform of Genomics based Drug Discovery

Study to promote the practical application of genomic information studies to medical care (study to solve problems concerning promotion of genomic drug developing studies)
A-②: Problem of feeding back genomic information to patients
“Study concerning the establishment of a system for appropriate disclosure of genomic information in clinical situations”

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Research	Mizuki	Graduate School of Medicine Dentistry and Pharmaceutical
Collaborator	Morita	Sciences, Okayama University
Research Collaborator	Eiji Nanba	Organization for Research Initiation and Promotion, Tottori University
Research	Naoki	Center for iPS Cell Research and Application, Kyoto
Collaborator	Harada	University
Research	Tomohiro	Clinical Genetics Unit/ Clinical Oncology, Kyoto University
Collaborator	Kondo	Hospital
Research	Masahiro	Kyoto University Hospital, Clinical Genetics Unit
Collaborator	Yoshioka	
Research	Yoshihiro	Clinical Oncology, Kyoto University Hospital
Collaborator	Yamamoto	
Research Collaborator	Nana Akiyama	Center for Medical Genetics, Chiba Children’s Hospital
Research	Yumie	Genetic Medicine and Services, National Cancer Center

Collaborator	Hiraoka	Hospital East
Research Collaborator	Eriko Takamine	Cancer Center/ Medical Genetics, Tokyo Medical and Dental University, Medical Hospital
Research Collaborator	Hidenori Kawasaki	Medical Ethics and Medical Genetics, Graduate School of Medicine of Kyoto University
Research Collaborator	Hiromi Murakami	Kyoto University Hospital, Clinical Genetics Unit
Research Collaborator	Masako Torishima	Kyoto University Hospital, Clinical Genetics Unit
Research Collaborator	Naoko Nakagawa	Medical Ethics and Medical Genetics, Graduate School of Medicine of Kyoto University

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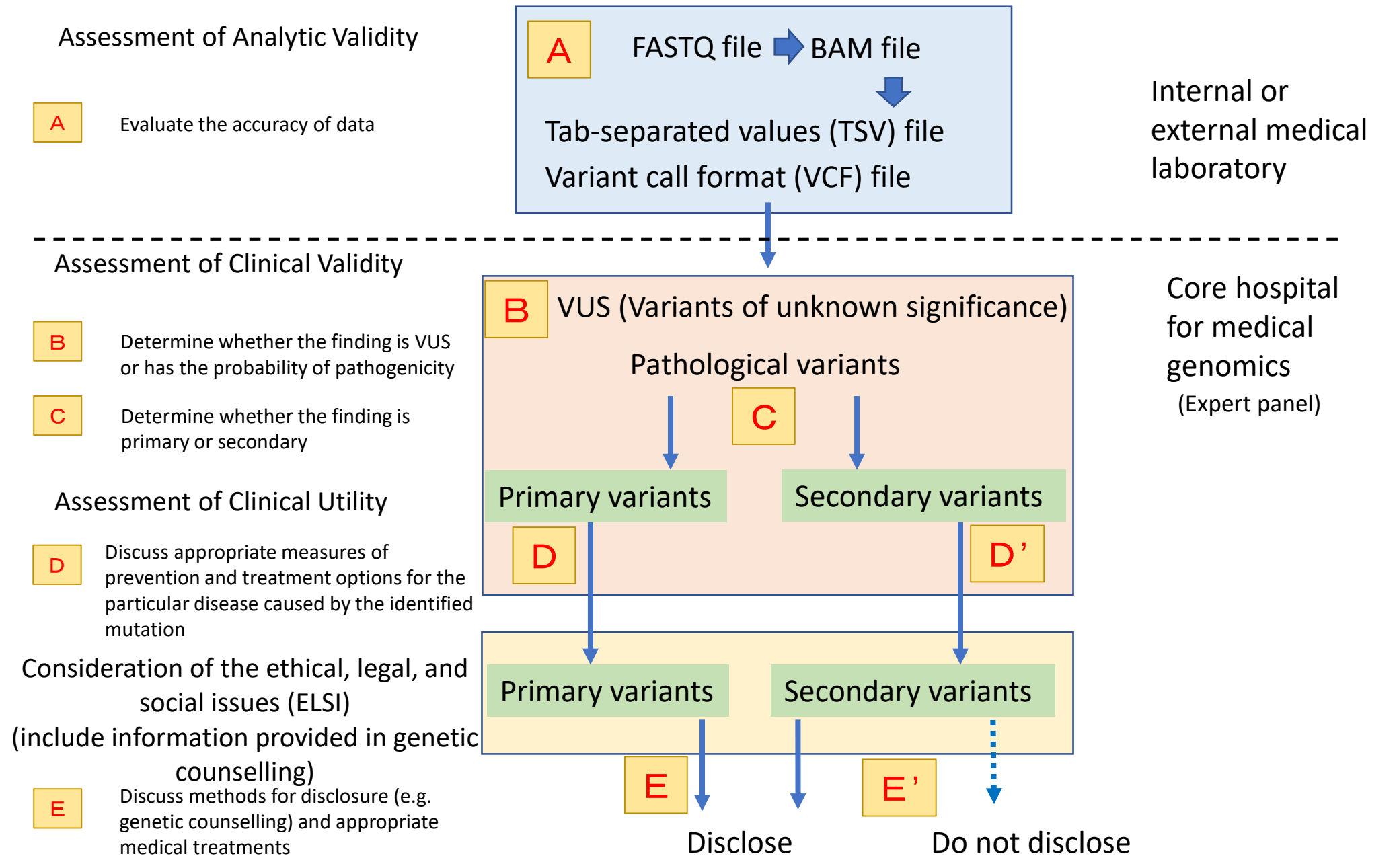
Appendix Table 1: Flow of procedures to be followed to provide information and obtain informed consent regarding secondary findings of tumor profiling testing

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

	T/N-pair testing	T-only testing
Discussion prior to the test	Discuss the possibility of secondary findings *	Discuss the possibility of secondary findings * and the need for additional tests to confirm secondary findings
Consent prior to the test	Confirm whether the patient would like to obtain secondary findings	Confirm whether the patient would like to know about possible secondary findings
Conduct the test	Test tumor tissues and blood	Test tumor tissues only
Expert panel	Determine whether there are secondary findings	Determine whether there are possible secondary findings and whether confirmatory tests can be performed
Disclose findings	Disclose primary and secondary findings (does not need to be simultaneous)	Inform of the possibility of secondary findings
Consent at the time of disclosure		Confirm whether the patient is interested in undergoing confirmatory tests for possible secondary findings
Perform confirmatory test		Perform confirmatory blood test
Disclose findings		Disclose secondary findings

*In this context, “secondary findings” refer to findings that should be made available to patients (i.e. medically actionable findings).

Appendix Figure 1. Flow for data obtained in NGS panel



Appendix Table 2: Members of the cancer genomics expert panel and their roles

◎: Core member, ○: Participation ideal, △: Optional

Process	Requirement for expert panel on provision of guidelines for infrastructures in core hospitals for cancer genomics. II21(2)②d(*): indicates that participation in the expert panel is not required but ideal.	(a) Oncologists	(b) Medical geneticists	(c) Genetic counsellors	(d) Pathologists	(e) Cancer genomics expert[#]	(f) Bioinformatician	(g) Primary physician	*Assistant, coordinator for genetic counselling	*CRC*	*Nurses involved in cancer treatment*	*Pharmacists involved in cancer treatment*	*Laboratory medical technologists and laboratory physicians involved in cancer treatment*
	Requirement by core hospital for cancer genomics	○	○	○	○	○	○	○	○				
A	To determine the accuracy of data	○			○	○	◎						○
B	To determine whether the finding can be categorized as	○	○	○		◎	○						

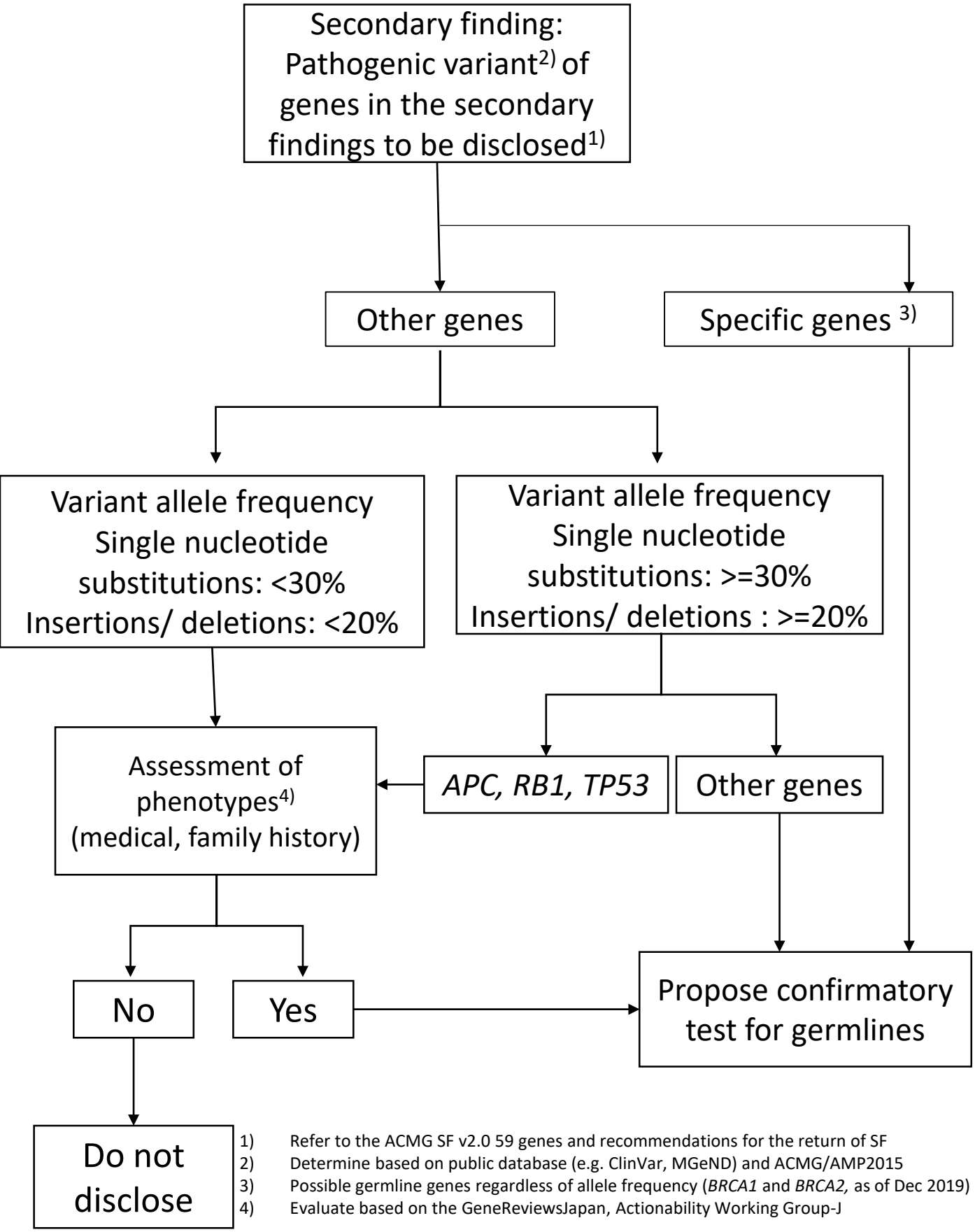
	VUS or has the probability of pathogenicity												
C	To determine whether the finding is primary or secondary	○	◎	○	△*	○		○					
D	To discuss appropriate measures of prevention and treatment options for the particular disease caused by the identified mutation	◎	○	○		○		○				○	
E	To discuss methods for disclosure (e.g. genetic counselling) and appropriate medical treatments	○	○	◎		○		○	○		○		

Individuals with expert knowledge of molecular genetics and cancer genomics

* If the initial test was limited to tumor cells, additional analyses (e.g. ratio of tumor cells) are needed to assess secondary findings

Appendix Figure 2

Operation guidelines for germline tests to confirm secondary findings from tumor profiling test of tumor cells



1) Refer to the ACMG SF v2.0 59 genes and recommendations for the return of SF
2) Determine based on public database (e.g. ClinVar, MGeND) and ACMG/AMP2015
3) Possible germline genes regardless of allele frequency (*BRCA1* and *BRCA2,* as of Dec 2019)
4) Evaluate based on the GeneReviewsJapan, Actionability Working Group-J