Guidelines for the Communication Process in Genomic Medicine

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

[Revised 2nd edition]

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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)
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"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