Proposal concerning the information transmission process in genomic medicine

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

[Revised edition]

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This proposal aims to cope with comprehensive germline genetic analysis using next-generation sequencing performed as a clinical test. However, as of 2019, germline genetic analysis is performed in Japan as a clinical test for only 79 diseases covered by national health insurance and approximately 180 diseases, including those by advanced medical care or without insurance coverage. In Japan, all comprehensive germline analyses, such as whole exome/whole genome sequencing using next-generation sequencing, are analyses performed as research, and the possibility that they are performed as true clinical examinations in the near future is not considered high. In this respect, the situation markedly differs from that of so-called tumor profiling testing.

In the United States and other countries, comprehensive genetic analyses, such as germline whole exome analysis, have been implemented as clinical tests for more than several years. In view of this, evaluation aiming for their clinical application is also necessary in Japan. In the Initiative on Rare and Undiagnosed Diseases (IRUD), which is an important research project of the Japan Agency for Medical Research and Development (AMED), germline whole exome analysis is performed on undiagnosed patients suspected of having inherited diseases, but it is performed as research and there is no feedback of secondary findings (Note 1). However, in the implementation of germline whole exome analysis performed as clinical tests for diagnosis, it is necessary to evaluate disclosure of clinically useful secondary findings. This proposal is made in anticipation of such.

Comprehensive germline genetic analysis performed for the diagnosis of patients suspected to have inherited diseases has characteristics different from those of tumor profiling analysis such as that the pathogenic significance of detected variants (base sequences with deviations from the reference sequence) relatively frequently remains unclear and that disease areas related to secondary findings may vary widely. It is necessary to make careful preparations before disclosure of the results, and if secondary findings requested to be disclosed are detected, it is essential to provide new medical care and refer the patient to an expert in the relevant disease area.

Comprehensive germline genetic analysis was hardly a reality 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 comprehensive germline genetic analysis markedly differs in nature compared with tumor profiling analysis, it is expected to develop as an important examination in all areas of medicine. Therefore, all persons and organizations, including related scientific societies, are required to maintain a high level of morality and respect, and properly respond to this proposal to make genomic medicine useful by

gaining the understanding and trust of patients, families, and society.

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

Comprehensive germline genetic analysis is performed at medical institutions or registered clinical laboratories as a clinical examination for the diagnosis based on the Medical Service Act and the Act on Clinical Laboratory Technician usually under national health insurance, but occasionally as a procedure not covered by insurance including advanced medical care.

① Whole genome analysis, such as whole genome sequencing, performed as a clinical test
② Whole exome analysis performed as a clinical test
③ Cross-disease group panel analysis performed as a clinical test
④ When the results of analyses corresponding to ①-③ above performed as part of research are confirmed as clinical test results and disclosed to the patient.

As the results of human genome/gene analysis studies belong to the subjects, they may be returned to them depending on the content of informed consent. However, as they are not the results of clinical tests, they must be handled carefully and appropriately with 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 this proposal must also be referred to in returning the results of such a study.

(2) Points of attention in pretest explanation

① In implementing comprehensive genetic analysis, it is necessary that a clinical section of medical genetics (an organization with a system for genetic counseling that can cooperate with other clinical departments) is established. Recommended setup conditions of a clinical section of medical genetics include a certified genetic counselor and multiple clinical geneticists working as full-time staff members, that conferences associated with a clinical section of medical genetics are held regularly, that the organization is a training facility of the clinical geneticist system, and that the organization 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, necessary clinical information, including the results of other clinical examinations, must be sufficiently collected, and possible general genetic examinations (chromosome tests, tests of candidate genes, and disease group panel tests) must be implemented, in principle, before comprehensive germline genetic analysis is evaluated. However, as it is more efficient to perform comprehensive analysis from the beginning depending on the situation, a flexible approach is recommended.

③ The primary objective of the analysis is to establish a previously unknown diagnosis, but as the results are information that can also be shared by relatives, explanation before implementation of the analysis must be conducted by taking sufficient time in close cooperation between 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 must also be provided.

④ As it is possible that primary findings affect the state of health, health management, or reproductive behavior of relatives and that secondary findings are detected, and because analyses may be performed simultaneously on the parents and siblings in addition to the patient, it is desirable to appropriately provide information to attendants such as family members, including parents and siblings.

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 the diagnosis of the present illness, 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 with sufficient explanation before the analysis, in principle (Note 3), 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 the primary or secondary findings are useful for the health management of relatives. (It is desirable that the "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 condition of the patient and comprehensive genetic analysis in advance, and are able to confirm the will about disclosure. This space may be left blank or be filled in later.)

⑧ Informed consent must be received from patients after they and their families have sufficiently understood the above contents.

⑨ In addition to the aspects mentioned above, comprehensive germline genetic analysis is considered to have a strong psychological and social impact because the possibility that primary findings are obtained is not necessarily high, there are times when definitive results

cannot be obtained, and there is the possibility that the parents are found to be presymptomatic or asymptomatic mutation carriers. In addition to these, pretest genetic counseling to discuss the reasons for wishing to be tested and expectations for the test is important.

⑩ 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 accent according to the patient's ability to understand.

(3) Contents of pretest explanation

① Checking the course and examinations performed until the present and their results, diagnostic process adopted by the attending physician, and reasons for proposing comprehensive genetic analysis

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

③ It is possible that the pathogenic mutation (pathogenic variant) responsible for the present symptoms is found (and its probability) or that it is not found (Note 4).

④ Establishment of the diagnosis is the basis for medical practice and comprehensive genetic analysis is an important examination necessary for the diagnosis. However, 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 is evaluated by maximum effort at present and based on the latest information, the interpretation may change in the future due to accumulation of novel knowledge with the development of research.

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

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

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

⑨ The primary findings (mutation responsible for the disease) obtained may be shared by relatives, and affect their state of health, health management, and reproductive behavior.

⑩ Pathogenic variants considered 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 coping methods (treatment or preventive method) for the expected phenotypes depending on the secondary finding.

⑫ There is the possibility that the secondary findings affect both the patient but relatives.

⑬ If secondary findings which are medically actionable, such as treatments/preventive measures considered useful for the health management of the patient/relatives (hereditary tumor or cardiovascular disease, etc.), are detected, the information can be used proactively. Not using such information may lead to disadvantages. However, the patient/relatives have the right to remain uninformed about it with sufficient understanding. Moreover, it is possible to make or change this decision 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 the analysis is also generated, it is practically impossible to evaluate all of them (accuracy of the data and probability of pathogenicity).

⑮ There are times when it is difficult to determine whether the findings obtained are primary findings related to the cause of the disease to be diagnosed or secondary findings unrelated to the disease.

⑯ If the patient is a child and if a secondary finding related to a disease with a late onset for which there are coping methods is detected, it is necessary to sufficiently discuss the psychological and social effects of disclosure because the finding does not have direct medical benefit for the child even if it is useful for the parents or relatives.

⑰ There are times when the test results (primary and secondary findings) exert psychological effects on the patient and family. It is desirable to have anticipatory guidance (Note 6) or consultation according to possible test results (Note 7) as pretest genetic counseling.

⑱ If the results of analysis performed as part of research (primary and secondary findings) are used for clinical practice as the results of a clinical examination, the explanation that tests for confirmation are considered must be provided upon participation in the study in compliance with this proposal. Tests for confirmation must be performed by sampling blood again, in principle, and at this time, the consent to tests for confirmation must be confirmed.

(4) Evaluation of test results

① It is desirable to hold conferences based on cooperation between the clinical department and the clinical section of medical genetics (expert panel) with the attending physician, experts

in the clinical field, and those versed in interpretation of the results of genetic testing, such as clinical geneticists and certified genetic counselors specializing genetic medicine/genetic counseling, as essential members and to evaluate the individual results of comprehensive germline gene analyses in an integrated manner among the participants. If necessary, experts in genetic testing in the specific field, analysts who were in charge of the actual genomic analysis, bioinformaticians involved in the relevant genomic analysis (genetic expert), nurses, and clinical laboratory technicians are requested to participate. As it is highly likely that an expert panel participated in by experts in the field related to the secondary findings cannot be organized at a single facility, it is necessary to set up a regional or national organization or network for comprehensive germline gene analysis.

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 to 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) considerations of ethical, legal, and social viewpoints (methods for disclosure of the results, methods for providing medical care) (Figure 1).

③ The expert panel must also evaluate how the test results (primary findings) should be disclosed to the patient (or surrogate) and relatives.

④ Although the principal task of the expert panel is to evaluate primary findings, regarding secondary findings, it must sufficiently discuss, with attention to different aspects of each gene, whether there are findings to be disclosed such as (5) below, whether tests for confirmation are necessary, what are the specific advantages associated with disclosure, and points of attention in and methods for disclosure. If necessary, discussions must be held with participation of experts in the department treating the disease related to the secondary finding or from other facilities.

⑤ If the results of analysis performed as part of research (primary and secondary findings) are disclosed as results of a clinical test, confirmation tests by a clinical laboratory using newly collected blood samples are necessary, in principle.

(5) 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 (Note 8)

③ Findings should not be disclosed if they are not sufficiently accurate or reliable about the pathogenicity, and may thus pose a psychologically 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[1)], the disclosure of which is recommended based on the severity of their effects on life and possibility of treatment/prevention.

⑤ If findings that can be used for the diagnosis of asymptomatic carriers have been obtained, they should not be disclosed, in principle, because they are not presently considered directly beneficial to the health management of the patients/relatives.

(6) Points of attention in disclosure of primary findings

① The wishes about disclosure of the results must be confirmed.

② The results must be disclosed in close cooperation among the attending physician or an expert specializing in the patient’s symptoms and specialists in genetic medicine such as a clinical geneticist and certified genetic counsellor.

③ The significance of the results for the patient and relatives must be carefully explained.

(7) Points of attention in disclosure of secondary findings

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

② If the patient wishes disclosure in advance, and if no secondary findings to be disclosed are detected, the patient must be so informed at the time of explanation of primary findings. It must be noted that the fact that no secondary findings to be disclosed have been detected does not mean their absence.

③ If there are secondary findings to be disclosed, they must be disclosed in an environment that can protect the privacy of the patient under a system that is staffed with appropriate members, including a clinical geneticist and certified genetic counselor, who can provide sufficient genetic counseling.

④ Cooperation with clinical departments and experts of the diseases related to the secondary findings in and out of the institution must be arranged. In particular, if the facility has no relevant expert, cooperation between the attending physician who has initiated the test and medical organizations related to the secondary findings must be arranged through a certified genetic counselor of the section of medical genetics using information of 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 of patients, families, and relatives

① For patients in whom primary or secondary findings have been obtained 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 genetic testing to examine whether relatives have the same variants must be established.

(9) Others

This proposal is not directly targeted to germline multi-gene panel analysis of disease group (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.

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

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 related laws and regulations.

(Note 1) Conventionally, the term “incidental findings/secondary findings” was often used, but this proposal proposes to separately refer to 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[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” and mentions “ACMG recommends that

laboratories conducting large-scale genetic sequencing for any clinical purpose should look for variants underlying 24 phenotypic traits" is given as an example. The ACMG recommendations[3] require separate assessment of 24 diseases (presently 59 genes related to 27 diseases[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 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[1] 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.

(Note 2) This proposal does not apply to prenatal diagnosis or diagnosis of embryonic tissue.

(Note 3) Concerning requests for disclosure of secondary findings, the wishes are heard before the test and confirmed before disclosure, in principle. It is also necessary to remind the patients that they have the right to retract their consent. In analyses as part of research, it is desirable to confirm the patient's wishes about tests for confirmation in advance in anticipation of a situation in which secondary findings are suspected, making tests for confirmation as clinical tests necessary.

(Note 4) In general, the diagnostic rate is approximately 25-40% by whole exome analysis and 50% by whole genome analysis.[4] The frequency of detection of germline mutations varies with the symptoms of those who are diagnosed, subject population, presence of familial history, and method for interpretation of pathogenic significance.

(Note 5) It is generally considered that germline mutations that correspond to secondary findings are detected at an overall frequency of a few percent by whole exome analysis, but the frequency varies with the definition of secondary findings and method for interpretation of pathologenic significance.[5-12]

(Note 6) Anticipatory guidance. Having the subject themselves think before the tests about changes in the feelings that may occur when informed of the test results and what specific measures there are to cope with them.

(Note 7) Presently, comprehensive germline gene analysis is often performed 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 the long-standing search for the cause (search for the diagnosis) (“end of diagnostic odyssey”), leading to clarification of future prospects, and a sense of relief and security. On the other hand, instances of increased 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) by the establishment of the condition as an genetic disease and prognostic information have also been reported. There are also reports that it is not necessarily the end of “diagnostic odyssey” but the beginning of a new “odyssey”. Moreover, the psychological and social effects of situations, such as a pathogenic variant not being detected or that the results are ambiguous need to be further investigated, and sustained genetic counseling after explanation of the results are important under the present circumstances regardless of the results.[4),13)-15)] Specifically, some patients and families are psychologically shocked, but others are relieved by the clarification of pathogenic variants. Moreover, some are relieved, but others are disturbed if pathogenic variants have not been detected. In addition, regarding secondary findings, there are times when friction may occur in the family about whether the patient should take the test or how to talk about the test or convey the test results, and when 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 must be evaluated carefully by the expert panel. The ACMG guidelines[16)] should also be referred for 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 the management methods have been proposed by different guidelines must be evaluated individually.

(Note 9) 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.

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