Japanese Association of Medical Sciences

Guidelines for Genetic Tests and Diagnosis in Medical Practice

February 2011
Revised March 2022

（The terminology used in this guideline regarding genetics is currently under review by the Working Group on Genetics Terminology Revision of the Terminology Management Committee of the Japan Medical Association, and may be changed in the future.）

Table of Contents

Introduction

The progress of medical genetics has enabled the elucidation of the pathogenesis and clinical conditions of monogenic diseases by identifying the responsible genes and progress of research aimed at the development of therapeutic strategies. Furthermore, research on medical genetics has brought about great achievements applicable in the fields of medicine and medical practice such as gaining insight into genetic factors associated with the onset of multifactorial disorders and individual variations in responses to pharmacotherapy. Various genetic tests and diagnoses based on the results of such tests (genetic testing and diagnosis) developed through this process have allowed the selection of appropriate treatments and prophylaxis for various diseases, and we are now living in an era where genomic medicine, which utilizes exhausting gene analysis techniques, is widely and effectively used in all areas of medical care. Thus, genetic testing and diagnosis has become an important medical practice for physicians in all specialties. From the perspective of medical safety and team medicine, medical records containing genetic information should be accessible to all medical professionals who need it. However, genetic information must be handled with particular attention because it remains as is throughout the individual's lifetime, can be used to predict diseases, and could also affect their biological relatives. An assumption that underlies this concept is that diseases and clinical conditions associated with genetic variations and genotypes should not be regarded as rare exceptions but as signs of human diversity and individual uniqueness and be treated and respected as such. In other words, preventing social disadvantages or discrimination on the basis of genetic or genomic information should be avoided. Moreover, genetic information should be handled confidentially and in accordance with the personal information protection laws.

The Japanese Association of Medical Science (JAMS) considers that in order to provide better medical care to the Japanese people, physicians and co-medicals should perform genetic testing and diagnosis appropriately and effectively in medical practice with the highest level of attention and consideration for the characteristics of genetic information. These recommendations are summarized by the JAMS in the "Guidelines for Genetic Tests and Diagnosis in Medical Practice," which discusses the basic issues and principles that should be followed by physicians and co-medicals for genetic testing and diagnosis.

Furthermore, because genetic tests of diseases, disease-groups, and medical fields or departments performing tests for them are diverse, each requiring unique attention and warnings, each medical society is recommended to draw up guidelines or a manual for each disease (group), field, or specialty in accordance with these guidelines. Physicians and co-medicals involved in genetic testing/diagnosis are requested to pursue appropriate medical practices as per these guidelines.

Furthermore, genetic testing for research should be performed in accordance with the guidelines related to the research.

1. Scope of the Guidelines

These guidelines shall apply to gene-based testing [Note 1], such as molecular genetic testing (DNA/RNA tests), chromosomal testing, and biochemical genetic testing, which utilize individual genetic information and diagnosis using genetic information. The term “genetic testing” in the guidelines refers to tests analyzing pathogenic variants, such as mutations or chromosomal abnormalities associated with germline alterations, and their related tests [Note 2]. In medical practice, handling of individual genetic information can be involved in genetic tests that are conducted not only for the diagnoses of patients who have already developed a disease but also for asymptomatic carrier testing, presymptomatic testing, susceptibility gene testing, prenatal genetic testing, preimplantation genetic testing, and newborn mass screening for congenital metabolic disorders.

Meanwhile, this guideline will also act as a reference in handling germline genetic information, which can also be covered in testing and diagnosis for identifying changes in genes associated with cancer and other diseases that are not passed on to future generations, differences in gene expression and chromosomal abnormalities.

2. Characteristics of genetic information that should be considered when conducting genetic testing and diagnosis

Special attention should be paid to the following characteristics of genetic information when a genetic test is performed, and a diagnosis is made based on the test result.

- It does not change throughout the individual’s lifetime.
- It is partially shared with biological relatives.
- The genotype or phenotype of biological relatives can be predicted with a relatively accurate probability.
- It is possible to make a diagnosis of asymptomatic carriers (who have almost no chances of developing the disease related to the pathogenic variant [mutation] in the future but possess the variant [mutation] and can pass it onto the next generation).
- It is possible to almost certainly predict the likelihood of future onset of a disease before it develops .
- It may be used for prenatal or preimplantation genetic testing.
- Inappropriate handling of genetic information can cause social disadvantages to the examinees and their relatives.
- Uncertainty is inherent in genetic testing. Uncertainty refers to possible changes in significance and individual variations to the onset, timing of onset, symptoms or severity of the disease predicted by a pathogenic variant (mutation) and that their clinical utility may change with the advancement of medical care and research.

3. Important points in the practice of genetic testing

While conducting a genetic test, it is necessary to understand that aspects important for the test are different depending on the subject and the purpose of the test. A list of items to be considered and explained at the time of testing is shown in [Table 1].

3-1) Genetic testing for the purpose of diagnosing patients who have already developed the disease

3-1)-(1) Preparation before conducting a genetic test

Genetic testing for patients who have already developed the disease is conducted mainly for the purpose of definitive diagnosis of diseases considered clinically likely and differential diagnosis of diseases to be examined. The tests are conducted if they are deemed useful from the perspective of clinical and medical genetics after deliberating about their analytical and clinical validity and clinical utility [Note 3] upon providing an explanation and obtaining the patient's consent. When multiple gene tests or comprehensive genetic testing is required, the order, indications, and limitations of the tests should be carefully determined from the clinical point of view. At an appropriate time prior to testing, the patient should be informed about the purpose and implications of the tests as well as the possible conditions after obtaining the results, which may affect their relatives. The patient should further be provided support so that they can independently decide whether to take the test with an adequate understanding of the points mentioned above.

It is also recommended to fully explain, discuss and obtain written informed consent in advance on potential secondary (incidental) findings from genetic testing that may detect variants that are not directly related to the patient's definitive diagnosis, and whether such findings should be disclosed to the patient.

In principle, the examinee's attending doctor should obtain the informed consent or assent (informed consent in adults, informed assent in the case of minors) before genetic testing, and if necessary, genetic counseling by an expert [Note 4] should be arranged to provide the patient with adequate support for decision-making.

3-1)-(2) How to disclose genetic testing results

The results of genetic testing must be documented in medical records in the flow of clinical care and be explained in a clear and simple manner. Diagnosis cannot be made on the basis of genetic testing results alone, but must be made by comprehensively evaluating clinical data as well. The results of genetic testing are not only useful for a confirmatory diagnosis but also can provide clinically useful information about the relationship between the genotypes and phenotypes linked to the result.

When a confirmatory diagnosis is obtained, it is important to provide ample information about the course, prognosis, therapies, and convalescence from the disease.

Particular attention should be paid to the interpretation and disclosure of results of genetic testing in the following situations.

1) When it is difficult to confirm a new variant and its pathogenic significance.
2) When the penetrance of disease is considered less than 100%
3) When a pathogenic variant (mutation) for which clinical utility is not yet established by extensive genetic testing is found

The clinical significance of such variants described above should be determined cautiously and explained to the patient as needed considering that the interpretations could change.

When a pathogenic variant (mutation) is found in a non-target gene that was unexpected from the phenotype in extensive genetic testing, the clinical utility should be considered and the patient's intention to disclose the results should be checked before considering the disclosure of results. 3-2)-(2) should also be considered.

When the penetrance is low but there seems to be pathogenic significance, the results should be disclosed to the patient after explaining thoroughly about low penetrance.

3-2) Asymptomatic carrier testing, presymptomatic testing, newborn mass screening, prenatal testing, and preimplantation genetic testing

3-2)-(1) Asymptomatic carrier testing

Asymptomatic carrier testing is usually for those who do not develop the disease and do not require treatment. Therefore, in principle, genetic testing should not be performed without the individual's consent unless there is a particular reason.

3-2)-(2) Presymptomatic testing

In the case of presymptomatic testing that enables the prediction of disease development beforehand with nearly 100% accuracy, the genetic test(s) should be performed after the examinee has sufficiently understood the information concerning the available preventive method(s) and therapies for the disease after onset. The same should be done for genes with low or unknown penetrance if there is a chance of some medical interventions being clinically useful. Regarding the disclosure of test results, the examinee should be given full explanation about the characteristics and natural history of the disease again and provided with appropriate medical information to maintain their health. In particular, while conducting the presymptomatic diagnosis of a disease for which preventive method(s) or effective therapies after onset are unavailable, care and support for the examinee's psychological health are indispensable before and after the test.

3-2)-(3) Newborn mass screening

For genetic testing in newborn mass screening, parents should be explained thoroughly about the test in advance. Patients with positive results should be referred to a specialist institution to receive genetic counseling and then undergo confirmatory genetic testing. On making a definitive diagnosis, it is important to provide information on genetic counseling, the disease, and treatments and provide support for the disease.

3-2)-(4) Prenatal genetic testing, preimplantation genetic testing

Prenatal genetic diagnosis, in a broad sense, includes methods involving cytogenetic, biochemical, and molecular genetics, as well as cytological and pathological methods, using fetal samples of amniotic fluid and chorionic villi, and non-invasive prenatal testing using maternal blood samples, and diagnostic imaging using ultrasound sonography.

Preimplantation genetic testing (PGT) is performed on blastomere and trophectoderm samples obtained from in vitro fertilization and microfertilization techniques using cytogenic and molecular genetic methods PGT is classified into PGT-M intended for avoiding serious genetic disorders, and PGT-A for aneuploidy and PGT-SR for structural rearrangement, which are intended for avoiding miscarriage by testing for chromosomal imbalance originating in aneuploidy and structural rearrangements that can cause infertility.

Prenatal genetic testing and preimplantation genetic testing have many medical, social, and ethical issues to be considered. When implementing these tests, the views of the Japan Society of Obstetrics and Gynecology and other related societies should be observed, the opinions of obstetricians and gynecologists, clinical geneticists, and pediatricians should be considered, and appropriate genetic counseling [Note 4] including psychological consideration and support for the examinee before and after the test should be provided. .

3-3) Genetic testing for minors and other persons incapable of consent

In the case of genetic testing of a disease that has developed in a minor or a person incapable of consent, it is necessary to obtain the consent of an individual standing as a surrogate representative. In this case, the surrogate should decide after a careful consideration of the examinee's beneficence in his/her health care. It is desirable to obtain assent from the examinee after giving the explanation of the test at a level corresponding to the patient's ability.

The same should be applied for genetic testing of diseases that develop before adulthood if their presymptomatic diagnoses are useful in the management of the examinee's healthcare.

Meanwhile, asymptomatic carrier diagnosis or presymptomatic testing for diseases that develop in and after adulthood in a minor should generally not be performed by the consent of the examinee's surrogate, but should generally be postponed until the minor reaches adulthood and is capable of taking autonomous decisions

3-4) Genetic testing for complex disease (disease susceptibility diagnosis)

An increasing number of genetic factors involved in complex diseases have been elucidated, and the development of genetic tests to prevent the onset of these diseases are anticipated. However, the tests used for the prediction of these complex disorders have the characteristics described below. It is necessary to understand the scientific basis of the analytical and clinical validity and clinical utility [Note 3] of the tests when they are implemented. Furthermore, physicians should also consider providing genetic counseling before the implementation [No.4] in case it is required.

- Multiple genetic factors are involved in a complicated manner in the development of complex diseases.
- The obtained result is the risk (probability) of the onset of disease.
- The ability of prediction of phenotype based on the genotype is not necessarily high.
- Not only genetic factors but also environmental factors are involved in the development of disease.
- The relative contribution of genetic and environmental factors differ for each disease.
- Genetic testing for complex diseases is generally observed for correlations rather than causation, and the clinical implications of the results are not always clear
- The genetic background of complex diseases can differ slightly depending on ancestry populations, and interpretations of the same test results can vary between individuals
- Diseases that are believed to be complex based on clinical findings could turn out to be a disease associated with a single gene pathogenic variant (mutation) by genetic testing

4. Handling personal information and personal genetic information

1) Protection of personal information

Healthcare professionals who have access to an examinee's genetic information are required to fully understand the characteristics of genetic information and handle personal genetic information appropriately in accordance with this guideline and conform to personal information protection laws.

2) Documentation on medical records

Germline genetic information stays constant throughout one's lifetime (static information), but it is simultaneously cross-organic information, which is shared by all the cells of the body. It is also shared not only by current biological relatives but also by future biological relatives. As such, genetic information must be shared between clinical departments and between physicians and co-medicals and stored for a long term to ensure sufficient protection of the patient's privacy. The results of genetic testing and content of genetic counseling should likewise generally be documented in medical records, similar to other clinical data.

3) Education and training of medical staff

All healthcare professionals who may have access to genetic information, which contains genetic characteristics in addition to other clinical information, should be educated and trained in terms of basic knowledge about genetics, confidentiality, and appropriate handling of personal genetic information.

4) Confidentiality obligations to the examinee and explanation of results to biological relatives

All personal genetic information obtained from genetic tests, as any other medical information, is subject to confidentiality and should not be disclosed to any third party, including the examinee's relatives without the consent of the examinee. However, when the genetic diagnosis of an examinee is

considered beneficial for the health management of the relatives of the examinee, disclosure of the genetic information to the relatives may be considered if it is impossible to implement effective prevention and treatment without such information. In doing so, the consent of the examinee would be necessary before disclosing the results to the biological relatives. However, considering the best interest of the examinee's relatives, genetic information of the examinee may be disclosed to their biological relatives to prevent disbenefits to them, even if the consent of the examinee cannot be obtained. In such cases, disclosure to the examinee's relative(s) should be performed not just based on the sole judgment of the attending doctor but through consultation with the ethics committee of the relevant medical institution.

5) Consideration for preventing social disadvantages and discrimination

All healthcare professionals should treat genetic information with the awareness that, similar to other sensitive information, this can lead to disbenefits or discrimination for the patient and relatives in various situations such as insurance, employment, marriage, and education. As with other medical information, inquiries from third parties, such as private insurance companies about the patient's health, cannot be answered without the consent of the patient. Informed consent should be obtained after providing a fair explanation of the benefits and disbenefits to the patient.

5. Genetic counseling [Note 4]

In implementing genetic tests/diagnoses, genetic counseling is performed at an appropriate time when necessary. Genetic counseling provides not only information but also psychological and social support so that the patient/examinee can autonomously make a decision. Therefore, it is desirable that the attending doctor with clinical experience of the disease cooperates with an expert in genetic counseling, and they practice as a medical team.

6. Conducting genetic testing

Genetic testing should be conducted by ensuring precision according to standards stipulated by regulations such as the Medical Care Act.

Endnote

In implementing genetic tests and diagnoses, it is important that physicians of each clinical division have sufficient understanding, knowledge, and experience in genetics. Because the information on genetic testing and diagnosis is continuously updated, physicians involved are encouraged to keep up with the latest research results in order to utilize such information for their medical practice. It is desirable that they cooperate with medical geneticists when necessary, taking into consideration the characteristics of the disease and the clinical area targeted for the genetic test. It is desirable that medical institutions fully comprehend the aims and contents of these guidelines so as to continue the education of healthcare professionals involved in genetic testing diagnosis with regard to the basic knowledge of medical genetics and the appropriate handling of individual genetic information. It is also desirable for medical institutions to construct a system for the appropriate implementation of medical genetics.

Medical genetics can make rapid progress and genetic testing is expected to be broadly applied in various medical fields. There is a need for each medical society that belongs to the Japanese Association of Medical Sciences to provide education regarding appropriate medical genetics and genetic counseling for diseases in each area of medicine.

These guidelines are subject to occasional revisions. Furthermore, the “Guidelines on Genetic Testing” by the 10 associations related to medical genetics (August 2003) will be discontinued.

[Note 1] Classification and definition of gene-based tests

Based on the proposal of "Technical Committee on Standardization for Gene-based Testing" established in the Japanese Committee for Clinical Laboratory Standards (JCCLS), the term "genetic test" is classified and defined as follows:

1) Pathogen nucleic acid test

A test to detect or analyze the nucleic acid (DNA or RNA) of foreign pathogens (viruses and microbes, including bacteria) that cause infectious diseases in humans

2) Human somatic cell genetic test

A test to elucidate the genetic information that changes along with the stage of the disease, localized to the disease-affected regions/tissues, including genetic analysis and gene expression analysis, to detect the abnormal structure of the gene unique to cancer cells.

3) Human genetic test

A test to elucidate the genetic information within a genome and mitochondria, which does not change throughout the individual's lifetime in principle and is passed onto the future generations (information that is clarified by genetic analyses of the germline). This includes genetic tests for monogenic diseases, multifactorial diseases, effects/side effects/metabolism of drugs, and information that could identify individuals.

1)–3) are collectively regarded as "gene-based tests," and the terms 1) pathogen genetic test, 2) human somatic cell genetic test, and 3) genetic test should be used in general.

[Note 2] Germline pathogenic variants (mutations) that are under the scope of this guideline

This guideline used the term pathogenic variant (mutations). Variants refer to individual differences in DNA base sequences and some signify the cause of a disease, others do not signify the cause of a disease, while some are unknown at present. There are two types of pathogenic variants (mutations): germline mutations and somatic mutations. The former is commonly present in all cells that form an individual and can be passed down to the next generation as genetic information. This mutation can be detected by testing any cell that constitutes the human body such as peripheral blood, skin fibroblast, hair, nail, and oral mucosa. The latter is a genetic mutation acquired in somatic cells after fertilization or birth, and it is not passed down to the next generation in principle. They are mainly observed in malignant tumors. In order to detect this mutation, it is necessary to directly test the cancer cells, tissue, or samples that contain the nucleic acid (DNA/RNA) derived from them (e.g., plasma, serum, urine, and cerebrospinal fluid). These guidelines cover the genetic tests for germline mutations in principle.

Even if the tests are used to detect differences in gene expression or chromosomal abnormality that occurs within cancer cells after fertilization and thus will not be passed down to the next generation, referring to these guidelines is essential if these aspects are possibly related to the genetic information of the germline. However, forensic DNA tests, such as determination of parentage, which is not in the framework of medical practice, is not covered by these guidelines.

[Note 3] Analytical validity, clinical validity, and clinical utility

1) Analytical validity refers to a condition where the test method has been fully established and appropriate quality controls have been performed for highly reproducible results. The evaluation is based on information such as presence of a positive rate when the subject has the pathogenic variant (mutation), a negative rate when the subject has no pathogenic variant (mutation), or the presence of a precision control program, which is the procedure of confirmation.
2) Clinical validity refers to the condition that adequate implications are given to the test results. The evaluation is based on information such as sensitivity (positive rate when the examinee has the disease), specificity (negative rate when the examinee has no disease), morbidity of the disease, positive predictive value, negative predictive value, or genotype–phenotype correlation.
3) Clinical utility refers to clinical merits, i.e., the target disease can be diagnosed by the test to improve patient and family understanding and acceptance of the disease, thereby obtaining information for the patient's future prospects including appropriate prevention and therapy. The evaluation is based on the effect the test result has on the examinee and providing effective support to the examinee.

[Note 4] Genetic counseling

Genetic counseling is a process to help people understand and adapt to the medical, psychological, and familial implications of genetic contributions of the disease. This process includes the following: 1) interpretation of the family history and medical history to evaluate the probability of disease occurrence or recurrence; 2) education on the genetic phenomena, test, management, prevention, resources, and research; and 3) informed choice (autonomous decision with sufficient information) and counseling for the promotion of the adaptation to risk and the actual condition.

It is desirable that all physicians acquire basic knowledge and skills for genetic counseling. In addition, physicians and medical institutes in charge of genetic testing and diagnoses should have a system in place to provide genetic counseling by specialists of physicians and non-physicians or refer them to a genetic counselor(s) as necessary.

Table 1. Examples of explanations to be considered at the implementation of the genetic test

---

1) Disease name: The disease name and clinical condition targeted for the genetic test
2) Epidemiological matters: Prevalence, morbidity, sex ratio, and ethnic differences
3) Pathophysiology: Known or estimated molecular genetic mechanism of the disease. When it is unknown, indicate the same.
4) Explanation of disease: Symptoms, age of onset, complications, and an accurate natural course, including prognosis
5) Therapy: Availability, effects, limitations, side effects of therapy, prevention, and early diagnosis and treatment method (surveillance method)
6) Genetic matters:
   - Mode of inheritance: Confirmed or estimated mode of inheritance
   - Penetrance, *de novo* mutation rate, and probability of germinal mosaicism
   - Recurrence rate: Recurrence rate in siblings and children (theoretical and empirical risk)
   - Genetic effect: probability that biological relatives are affected or are carriers
7) Genetic testing
   - Purpose of the genetic test (significance of genetic test for the patient who has already developed the disease): Name of the gene targeted by the test and its characteristics, and so on
   - Method of the genetic test: Method for specimen collection, technology employed in the genetic analysis, and so on
   - Probability of definitive diagnosis by the genetic test: accuracy of the test, difference in detection rate by the testing method, and so on
   - What more can be known by the genetic test: genotype–phenotype correlation
   - Disclosure method of the result of the genetic test: how and to whom the result is disclosed
   - Possibility, outline and significance of asymptomatic carrier diagnosis, presymptomatic diagnosis and prenatal diagnosis of relatives based on the information obtained from the genetic test of the patient
8) Information regarding social resources: medical expenses compensation system, social-welfare system, patient support group information
9) Providing genetic counseling
10) Characteristics of genetic information
   - Does not change over an individual's lifetime
   - Genetic information is partially shared among biological relatives
   - Genotype and phenotype of relatives can be predicted with good accuracy
   - It allows predicting future disease onset in advance
   - Disclosure of the results of genetic testing performed for the definitive diagnosis of a patient already showing signs of symptoms to the relatives should be actively considered, when the obtained individual genetic information can be beneficial for the relatives.

・Uncertainty is inherent in genetic testing. Uncertainty refers to possible changes in the significance and individual variations in the onset, timing of onset, symptoms, or severity of the disease predicted by a pathogenic variant (mutation) and that their clinical utility may change with the advancement of medical care and research.

11) The rights of the examinee

- The examinee is free to decide whether or not to undergo the genetic test, to discontinue the test, or to refuse the disclosure of the result.
- The examinee will not receive any disadvantage or unfair treatment in future medical care by refusing or discontinuing the test, or refusing to hear the results and will be provided the best feasible medical care
- The examinee is presented with available options both before and after the test, and the merits and demerits of each option are explained in terms that are easily understandable.

(Note: It is not necessary that all the matters listed above should be explained to an examinee before the implementation of the genetic tests. These can be used for reference in explaining the test in accordance with the examinee's degree of understanding and characteristics of the disease.)