Introduction

The progress of medical genetics has made it possible to clarify the pathogenesis and clinical condition of monogenic (single-gene) diseases based on the identification of the responsible genes. It has also led to the advancement in research aimed at the development of therapeutic strategies. Moreover, research on medical genetics has brought about broad achievements applicable in the fields of medicine and medical practice such as the clarification of genetic factors associated with the onset of multifactorial disorders, individual variations in pharmacological responses, and so on. The techniques of genetic tests and diagnoses (genetic tests/diagnoses) developed in the processes have opened a new era when they can be utilized in all areas of medicine, and provide appropriate selections in the treatments and preventive methods of diseases. In this manner, genetic tests/diagnoses have become one of the most important medical practices for physicians of all specialties. Meanwhile, special attention needs to be taken in handling genetic information, since it does not change throughout the individual’s lifetime, and could also affect their biological relatives (further referred simply as relatives). An assumption underlying it is that diseases and clinical conditions based upon genetic variations, and genotypes should be regarded as human diversities and not as rare exceptions. Both human diversity and identity should be respected.

The Japanese Association of Medical Science (JAMS) considers that in order to provide better medical care to the Japanese people, physicians, co-medicals and individuals involved in genetic medicine should implement genetic tests/diagnoses appropriately and effectively in medical practice, giving the highest attention to and thoughtful consideration in the characteristics of genetic information. JAMS proposes here, in “Guidelines for Genetic Tests and Diagnoses in Medical Practice”, the basic issues and principals that should be observed when implementing such genetic
tests/diagnoses.

Since genetic tests of diverse diseases and disease-groups have been carried out in a wide range of medical fields or departments, genetic tests include certain points to keep in mind that are unique to each case. Hence, it is recommended that each medical society that belongs to JAMS should 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 test/diagnosis are requested to pursue appropriate medical practices according to these guidelines.

Regarding genetic tests in research, they should be performed in accordance with the guidelines related to the research.

1. **Scope of these guidelines**
These guidelines shall apply to genetic tests of human genome/genes including molecular genetic tests (DNA/RNA tests), cytogenetic tests, biochemical genetic tests (Note 1), and diagnoses using genetic information. The term “genetic tests” in the guidelines means those analyzing germline alterations such as mutations or chromosomal abnormalities, or those related to germline alterations (Note 2). In medical practice, genetic tests are carried out not only for the diagnoses of patients who have already developed a disease, but also for carrier detection, pre-symptomatic diagnosis, genetic predisposition tests, pharmacogenetic diagnosis, prenatal diagnosis, and newborn mass screening for congenital metabolic diseases.

Meanwhile, the guidelines do not cover genetic tests to identify gene mutations, gene expression, or chromosomal abnormalities which are confined to somatic cells such as cancer cells, because they occur after birth and will not be conveyed to the next generation. However, the tests and diagnoses should refer to these guidelines if there is a possibility that the results could be related to the germline genetic information of the individual.

2. **The characteristics of genetic information; important issues for genetic testing and its use in 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.
• Genotype or phenotype of not only the individuals tested (further referred to as examinees) but also their relatives can be predicted with a relatively accurate probability.
• It is possible to make a diagnosis of non-progressive carriers (who will rarely develop the disease in the future, but possess a mutated gene, and the mutation may possibly be passed down to the next generation).
• It may be possible to predict the development of disease beforehand with almost 100% accuracy.
• It may be used for prenatal diagnosis.
• If it is inappropriately handled or disclosed, it may cause a social disadvantage to the examinees and their relatives.

3. Important points in the practice of genetic testing
When conducting a genetic test, it is necessary to understand that important points in the test are different depending on the examinee and the purpose of the test. A list of the explanatory items to be considered at the implementation is shown in Table 1.

3-1) Genetic testing for the diagnoses of patients who have developed a disease.
Genetic testing for the patients who have already developed a disease is conducted mainly for the establishment of confirmed diagnosis that is highly suspected from clinical information, or for the differential diagnosis that should be examined. The tests are conducted if they are judged to be useful from clinical and genetic medical perspectives after the deliberation of their analytical and clinical validity, and clinical utility (Note 3). If an examinee requires multiple genetic tests, the scopes and the order of the tests to be run should be thoughtfully determined from the clinical point of view. At an appropriate time prior to the testing, the examinees should be informed about the purpose and implication (including expected merits and demerits to the examinees) of the tests as well as the possible conditions after the results will be obtained and the fact that the genetic information gathered by the tests may influence their relatives. The directing physicians should confirm that the examinees have fully understood these matters, and support their autonomous and independent decision on whether or not to undergo genetic testing. It is recommended to obtain a written informed consent from
the examinees after the explanation and support. In principle, the examinee’s attending
doctor should perform the informed consent or assent before genetic testing, and if
necessary should arrange genetic counseling of an expert (Note 4) so that the examinee
can receive support for autonomous decision-making.

The results of genetic tests should be simply and clearly explained to the
examinees so that they can fully and adequately understand the results following a flow
of diagnosis. A diagnosis should not be made from the result of genetic examination
alone, but be established comprehensively from the clinical and genetic information. It
should be noted that genetic tests are helpful not only for the establishment of diagnosis,
but also for the medical practice using the information concerning genotype-phenotype
correlation brought about from the results. However, in the cases where it is difficult to
establish the pathologic significance of a novel mutation and where the penetrance of
disease is considered to be less than 100%, special attention is required in the
interpretation of the results. When a confirmed diagnosis is established, it is important
to provide the patient with sufficient information concerning the progress, prognosis,
therapy and medical care of the disease.

3-2) Genetic testing for non-progressive carrier diagnosis, pre-symptomatic diagnosis
and prenatal diagnosis
The genetic tests performed for the purposes of non-progressive carrier diagnosis,
pre-symptomatic diagnosis and prenatal diagnosis should be conducted after an
appropriate genetic counseling session (Note 4).

3-2)-(1) Diagnosis of non-progressive carrier
Non-progressive carriers do not develop a disease and thus normally require no
treatment. Therefore, genetic testing of their diagnosis should not be done without the
examinee’s consent unless there is a special reason.

3-2)-(2) Pre-symptomatic diagnosis
In the case of a pre-symptomatic diagnosis that enables the prediction of disease
development beforehand with almost 100% accuracy, the genetic test(s) should be
performed after the examinee has sufficiently understood the information concerning
the available preventive method(s) and therapeutic strategies of the disease. On the
disclosure of test results, the examinee should be given full explanation about the characteristics and natural history of the disease again, and should be provided with appropriate medical information to maintain the examinee’s health. In particular, when conducting a pre-symptomatic diagnosis of a disease for which preventive method(s) before, or effective therapies after the onset are unavailable, the care and support for the examinee’s psychological health are indispensable before and after the test.

3-2)-(3) Prenatal diagnosis
Prenatal diagnosis, in a broad sense, includes methods involving cytogenetic, biochemical and molecular genetics, as well as cytological and pathological methods, using fetus samples such as amniotic fluid, chorionic villi etc.; pre-implantation genetic diagnosis; and diagnostic imaging using ultrasound sonography. Because prenatal diagnosis holds many medical, social and ethical issues to be considered, the test/diagnosis should be performed complying with the views of the Japan Society of Obstetrics and Gynecology and others, and after providing the examinee with appropriate genetic counseling (Note 4).

3-3) Genetic testing for a minor, or a person incapable of his/her own autonomous decision-making.
In the case of genetic testing of a disease that has developed in a minor or a person lacking the ability to make his/her own autonomous decision, it is necessary to obtain the consent of an individual standing as a surrogate representative. In this case, the surrogate should decide after a thoughtful consideration of the examinee’s beneficence in his/her health care. It is desirable to obtain an assent from the examinee after giving the explanation of the test at a level corresponding to the patient’s ability.

The same is true for genetic testing of diseases that develop before adulthood if their pre-symptomatic diagnoses are useful in the management of the examinee’s healthcare.

Meanwhile, genetic testing in a minor for the non-progressive carrier diagnosis or the pre-symptomatic diagnosis of diseases that may develop in and after adolescence should not be performed in principle by the consent from the examinee’s surrogate, but should be postponed until the examinee reaches adulthood and becomes able to independently make a decision.
3-4) Pharmacogenetic tests
A pharmacogenetic test (Note 5) included in pharmacogenomic tests analyzes the
genetic variations in the germline. Because the genetic information obtained by the test
has the unique characteristics as undermentioned, the information can be dealt, in a
different way from the genetic information of monogenic diseases, as ordinary clinical
information in medical practice by referring to the related guidelines (Note 5).
• It can be used to avoid drugs that bring about dangerous side effects or drugs that have
  little effect to the examinee.
• Appropriate dosing amount can be estimated.
• The estimating abilities of the phenotype based on genotype are not necessarily high.

3-5) Genetic testing for multifactorial diseases (genetic predisposition diagnosis)
An increasing number of genetic factors involved in multifactorial diseases have been
elucidated, and genetic tests for these diseases to prevent their onset are expected to be
developed for clinical application. The tests used for the prediction of these
multifactorial disorders have the characteristics described below. It is necessary to
clarify the scientific grounds of the analytical and clinical validity, and clinical utility
(Note 3) of the tests when they are implemented in clinics. Directing physicians should
also consider before the implementation how to provide genetic counseling (No.4) in
case it is needed.
• Multiple genetic factors are involved in a complex manner in the development of
diseases.
• The obtained result is the risk (probability) of the onset of disease.
• The power of prediction of phenotype based upon the genotype is not necessarily
  high.
• Not only genetic factors but also environmental factors are involved in the
development of disease.
• Contribution degrees of genetic and environmental factors differ for each disease.

4. Handling of individual information and individual genetic information
Physicians and co-medicals accessing an examinee’s genetic information are required to
fully understand the characteristics of genetic information and handle individual genetic
information appropriately.

If a genetic test is performed for diagnosis of an examinee already showing signs of symptoms, the test results should be recorded in the medical documents as any other clinical test, and should be in principle shared by all physicians and healthcare experts involved in the care of the examinee.

All individual genetic information obtained from genetic tests, as any other medical information, is subject to confidentiality, and it should not be disclosed to any third party including the examinee’s relatives without the consent of the examinee.

When the genetic diagnosis of an examinee is 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 principle, the consent of the examinee would be necessary in such cases. However, considering the best interest of the examinee’s relatives, the examinee’s genetic information may be disclosed, even if the consent of the examinee cannot be obtained. Disclosure to the examinee’s relative should be performed not by the attending doctor’s sole judgment, but through consultation with the ethics committee of the relevant medical institution.

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.

In case the content of genetic counseling can infringe on the privacy issue, thoughtful response is required, for example, by describing and keeping the contents of counseling separate from the usual medical record.

Conclusion
In implementing genetic test/diagnosis, it is important that the attending doctors of each clinical division should have enough understanding, knowledge and experience in genetics. Because the information on genetic test/diagnosis is continuously updated, the
doctors 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 institutes fully comprehend the aims and contents of these guidelines, to continue education/enlightenment of not only physicians but also healthcare experts and co-medicals involved in the genetic test/diagnosis regarding the basic knowledge of medical genetics and the appropriate handling of individual genetic information. It is also desirable for medical institutes to construct a system for appropriate implementation of genetic medicine.

The field of 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/enlightenment regarding the appropriate genetic medicine and genetic counseling for the diseases in each medical area.

These guidelines are subject to occasional re-review.
(Note 1) Classification and definition of gene-based tests
Based upon the proposal of “Gene-related Test Standardization Experts Committee” established in the Japanese Committee for Clinical Laboratory Standards (JCCLS), a Specified Nonprofit Corporation, the term “genetic test” is classified and defined as follows:

1) Pathogen genetic test (Nucleic acid test)
A test to detect and/or analyze the nucleic acid (DNA or RNA) of foreign pathogens (viruses and microbes including bacteria) that cause infection to humans

2) Human somatic cell genetic test
A test to clarify genetic information that changes along with the stage of the disease and is limited to the disease affected regions/tissues, including genetic test or gene expression analysis to detect abnormal structure of the gene unique to cancer cells.

3) Human genetic test
A test to clarify genetic information within the genome and mitochondria which in principle does not change through the individual’s lifetime and is individually possessed by nature (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 in general the terms 1) pathogen genetic test, 2) human somatic cell genetic test and 3) genetic test should be used.

(Note 2) Germline mutation covered by these guidelines
There are two types of genetic mutations; namely 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 in principle passed down to the next generation. They are mainly observed in malignant tumors. In order to detect this mutation, it is necessary to directly test the cancer cells or tissue. These guidelines cover the genetic tests for germline mutations in principle.

Even if the tests are to detect differences in gene expression or chromosomal
abnormality that occurred within cancer cells after fertilization and thus will not be passed down to the next generation, it is necessary to refer to these guidelines if it is possibly related with 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
Analytical validity refers to, for example, 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 upon such information as the positive rate when the subject has mutation, the negative rate when the subject has no mutation, the presence of quality control program, the procedure of confirmation and so on.

Clinical validity refers to the condition that enough implications are given to the test results. The evaluation is based upon such information 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, genotype-phenotype correlation and so on.

Clinical utility refers to clinical merits, i.e. the target disease can be diagnosed by the test, thereby obtaining information for the patient’s future prospects including appropriate prevention and therapy. The evaluation is based upon the influence of the test result to the examinee, and 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 to 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 enough information) and counseling for the promotion of the adaptation to risk and the actual condition.

At present, there are two institutions for the training of genetic counselors; “Japanese Board of Medical Genetics, Clinical Geneticist” <http://jbmg.jp/> targeting medical doctors, and “Certified Genetic Counselor” <http://plaza.umin.ac.jp/~GC/>
targeting non-medical doctors, both of which the Japan Society of Human Genetics and
the Japanese Society for Genetic Counseling cooperatively certify.

It is desirable that all medical doctors acquire basic knowledge and skills for
genetic counseling. Medical doctors and medical institutes involved in genetic
tests/diagnoses should be prepared to provide genetic counseling or introduce a genetic
counselor(s) when necessary.

(Note 5) Pharmacogenomic test and pharmacogenetic test
“The Terminology of pharmacogenomics” (Ministry of Health, Labour and Welfare)
defines Pharmacogenomics (PGx) and Pharmacogenetics (PGt) as “a study on the
variation of DNA and the characteristics of RNA associated with response to drugs” and
“a part of pharmacogenomics, and a study on the mutation of DNA sequence associated
with response to drugs”, respectively. According to these definitions, not only the
analysis of the gene mutation of germline but also those of the somatic gene mutation of
tumor cells and gene expression within cells are included in Pharmacogenomics (PGx).

Based upon the definitions described above, these guidelines define and cover
tests handling genetic information of germline in association with response to drugs as
pharmacogenetic tests. The guidelines, associated with these tests include “the
operational guidelines of the pharmacogenomics test” and “the guideline for the clinical
research and test with the application of pharmacogenomics.”
Table 1. Examples of explanatory matters 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, difference among ethnicity, and so on
3) Pathophysiology: Known or estimated molecular genetic mechanism of disease. When it is unknown, indicate such fact.
4) Explanation of disease: Symptoms, age of onset, complications and accurate natural course including prognosis
5) Therapy: Availability, effects, limitations or 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, mutation rate and probability of germinal mosaicism
   • Recurrence rate: Recurrence rate of the siblings and children (theoretical and empirical risk)
   • Genetic effect: probability that biological relatives are affected or carriers
7) Genetic test
   • Purpose of the genetic test (significance of genetic test for the patient who has already developed 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 of 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 non-disease carrier diagnosis, pre-symptomatic diagnosis and prenatal diagnosis of relatives based upon 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, and so on

9) Availability of genetic counseling

10) Characteristics of genetic information

- Genetic information is partially shared among biological relatives
- The results of genetic test performed for definitive diagnosis of a patient already showing signs of symptoms should positively considered to be disclosed to the relatives, when the obtained individual genetic information can be beneficial for the relatives.

11) The rights of the examinee

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

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(Note: It does not necessarily follow that all the matters listed above should be explained to an examinee before the implementation of the genetic tests. These are for reference in explaining the test in accordance with the examinee’s degree of understanding and characteristics of the disease.)
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