“GUIDELINES FOR GENETIC TESTING”

Genetic-Medicine-Related Societies:

(alphabetically)

Japan Society of Human Genetics
Japan Society of Obstetrics and Gynecology
Japan Society for Pediatric Genetics
Japanese Society for Familial Tumor
Japanese Society for Gene Diagnosis and Therapy
Japanese Society for Genetic Counseling
Japanese Society for Inherited Metabolic Diseases
Japanese Society of Laboratory Medicine
Japanese Society for Mass-screening
and
Japanese Teratology Society

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PREFACE

Advances in cytogenetics, biochemical genetics, and molecular genetics have all made great contributions to the development of genetic medicine. Consequently, chromosomal and genetic-biochemical analyses as well as DNA-based testing have been used clinically as a part of laboratory tests. We expect that genetic information from such testing will play an increasingly important role in diagnosis, treatment, prevention, and genetic counseling modalities.

On the other hand, because the testing conveys important genetic information that remains unchanged through an individual’s life time, there are some important issues for discussion, such as informed consent at testing, protection of an individual’s genetic information, handling of specimens used in testing, and genetic counseling before and after testing [1, 2, 3]. In addition, as individual’s genetic information reflects genetic characteristics involving not only the individual but also the individual’s relatives, the establishment of new bioethical standards is required. Furthermore, genetic testing is recently taking place in medical and business settings in some medical facilities or companies without sufficient knowledge of medical genetics, technological basis for molecular genetics, its defined clinical implications, or establishment of any responsible systems. We are thus very much concerned about this kind of irresponsibility, because it brings only anxiety and distrust from the general public [4].

In the context of the rapid progress of the human genome project and possible expansion of applications of its achievements to medicine, bioethical guidelines and principles for basic and clinical human gene-based researches have already been established by the government. First, in April 2000, in conjunction with the “Millenium Project”, the Ministry of Health and Welfare’s Task Force on “Review and Critical Study

of Advanced Medical Technology" created "Guidelines for Human Gene Research and Its Related Ethical Issues" [5]. In June, 2000, the Bioethics Committee, Council for Science and Technology Policy in the Cabinet Office issued the "Fundamental Principles of Research on the Human Genome" [6]. In addition, in March 2001, using the afore mentioned "Fundamental Principles…" as a keystone, "Guidelines for Research on the Human Genome and Genes" was created for use in basic research settings. These are known as the "Three Ministry Guidelines" [7], as proposed in concert by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), the Ministry of Health, Labor and Welfare, and the Ministry of Economy, Trade and Industry. At present, human gene and genome research is conducted under these "Three Ministry Guidelines".

Gene-based data accumulated from human gene and genome researches are increasingly and effectively being used in clinical practice. Although it is not always easy to differentiate genetic testing from gene analysis aimed at basic research, genetic testing may also have various ethical, legal and social implementations (ELSI) when applied for clinical practice. Thus, there has long been awareness of the necessity for the establishment of guidelines for genetic testing, for appropriate clinical applications. Already in Japan, the Japan Society of Human Genetics has established, "Guidelines for Genetic Counseling and Prenatal Diagnosis (1995)" [8], "Guidelines for Genetic Testing, using DNA Analysis (1995)" [9] and "Guidelines for Genetic Testing (2001)" [10]. The Japanese Society for Familial Tumor has also proposed, "Guidelines for Genetic Testing and Research on Familial Tumors and Their Clinical Applications" (2000) [11]. In addition, in 2001, eight genetic-medicine-related societies, i.e., Japan Society of Human Genetics, Japan Society of Obstetrics and Gynecology, Japan Society for Pediatric Genetics, Japanese Society for Familial Tumor, Japanese Society for Gene Diagnosis and Therapy, Japanese Society for Genetic Counseling, Japanese Society for Inherited Metabolic Diseases, Japanese Society of Laboratory Medicine, Japanese Society for Mass-screening, and Japanese Teratology Society, have embraced the basic principles found in these guidelines and further established the "Proposed Guidelines for Genetic Testing (2001)". Relatedly, the Japan Registered Clinical Laboratories Association created "Ethical Principles on Entrusted Genetic Testing (2001)" [12], and the Japan Medical Association presented "Gene-based Medicine and Community Health" as a report of its 8th Meeting of Medical Ethics Council [13].

We, ten genetic-medicine-related societies, propose here a new version of "Guidelines for Genetic Testing" with the aim to incorporate testing in clinical practice, to expand previous guidelines established by these academic organizations, and to establish the basis of genetic medicine in the future. All members of the ten societies respect these guidelines and will conduct genetic testing in accordance with these guidelines. At the same time, those outside the societies, medical research institutes, medical facilities, laboratory testing companies, genetic analysis laboratories, their intermediary companies, health-related industries and mass-media, are asked to comprehend the implications of genetic testing and to abide by these guidelines. Furthermore, these guidelines also imply respect for the spirit in which these principles were established. We pledge to work towards accord in ELSI arising from genetic testing, even as our knowledge of genetics and biotechnology broadens. It is our great hope that genetic testing will bring vast new benefits to human health and welfare.

With future progress in genetic medicine and genetic testing, it is hoped that these guidelines also move forward, subject to appropriate and timely revision.

GUIDELINES FOR GENETIC TESTING

I. Testing to be directed by the guidelines

These guidelines concern genetic testing (chromosome analysis, biochemical testing and DNA-based testing) for gene mutations, chromosomal aberrations or their related germline abnormalities. The tests include those for clinical diagnosis, carrier detection, presymptomatic diagnosis, disease susceptibility estimation (including so-called diathesis diagnosis), pharmacogenetic diagnosis, prenatal diagnosis, and newborn screening for inborn errors of metabolism . However, the guidelines do not cover tests for gene mutation, gene expression and chromosome abnormality which are confined to somatic cells such as cancer cells nor those for infectious agents, e.g., bacteria and viruses, and DNA testing for forensic medicine such as determination of parentage (paternity testing).

II. Practice of Genetic Testing

1. Genetic testing should be carried out only when considered clinically and genetically appropriate and useful, as a part of comprehensive genetic medicine systems [see Note 3].

(1) Medical facilities that offer genetic testing must provide systems for comprehensive genetic medicine, including genetic counseling.

(2) When performing genetic testing, its analytical and clinical validity, and clinical utility that stand at the sufficient levels should be guaranteed.

(3) Facilities that carry out genetic testing must conscientiously pursue new data in medical genetics and concordantly must show a measurable improvement in diagnostic accuracy.

(4) Because of technological ease of sampling, genetic testing may be able to be performed by-passing standard medical procedures such as blood sampling. Nevertheless, genetic testing by-passing medical facilities should never be performed.

2. Those health-care professionals involved with genetic testing and its related genetic counseling should take great care to respect the human rights of individuals of being tested (further referred to as examinees) and their relatives and family members. All efforts should be made to protect examinees and/or relatives from possible discrimination (genetic discrimination) on the basis of their genetic information, such as specific karyotypes (chromosome constitutions), genotypes, haplotypes and/or phenotypes. In addition, all efforts should be made to offer appropriate medical care, clinico-psychological and societal support to these individuals.

3. The directing physicians involved with genetic testing should obtain informed consent on the genetic test from examinees prior to the testing.

(1) Informed consent requires understandable explanations of the following elements to examinees: the purpose, method, implications (including expected merits and demerits to examinees), accuracy (particularly regarding unavoidable diagnostic limitations), alternative choice other than the testing, and accurate information on any discomfort and/or medical risks of the testing. All these require written explanation in addition to oral explanation.

(2) Decision on whether or not to undergo genetic testing should be made on the basis of a free right of autonomy for examinees. The directing physicians should explain the individual rights of not being tested, the freedom to withdraw at any time, and to refuse disclosure of data after testing. Also individuals being tested must be informed that they have the right to receive unrestricted health care, even if their decision is not to participate or to withdraw from the test process. However, in these cases, it should be explained that the medical benefits that may be available from genetic testing will not be used as a treatment modality. Physicians are enjoined to offer the most appropriate medical care while respecting the decisions of examinees.

(3) In the instance of minors incapable of their own autonomous decision making, the consent of an individual standing as a surrogate representative should be sought. However, in this case, all efforts should be made to gain understanding of the examinees themselves, and careful judgment is necessary for the choice of the surrogate. The surrogates may include those with parental authority, legal guardianship, or those retaining

guardianship, and they must strive to protect the future beneficence of the examinee to the furthest extent possible.

(4) In the process of informed consent and explanations about the principles of inheritance, the directing physicians should strive to explain that a part of the genetic information gathered in testing is shared by examinees' relatives. In addition, the physicians must make efforts to gain understanding of examinees on the active disclosure of genetic information to their relatives, when the information becomes useful for their medical care.

4. Genetic testing may not be indicated in the following cases:
(1) When the directing physicians conclude that a test is ethically and/or socially inappropriate, or when against their personal, moral, ethical principles, the physicians may, with thorough explanations, refuse to carry out the genetic testing, even though examinees request it. Instead, the physicians should seek to introduce examinees to other alternative health-care providers.
(2) Pediatric genetic testing for an adult-onset disease that has no preventative or therapeutic options should be fundamentally avoided.
(3) In view of protection of future individual's autonomous decision making, genetic testing in minors should be postponed until adulthood, except for diseases for which therapeutic and/or preventive options are available based upon test results, or for urgent cases.

5. In principle, samples obtained for genetic testing (further referred to as samples) should not be used for purposes other than the test at hand.
(1) In the case where samples are expected to be used for other genetic tests that may be of potential future benefit to examinees or their families, new informed consent on storing of samples should be obtained with clear explanation of the implications of the tests and sample storing method.
(2) When stored samples are used for new genetic testing, new informed consent for the new testing should be obtained.
(3) When samples obtained for genetic testing are used for research, ""Guidelines for Research on Human Genome and Gene" (published jointly by the Ministry of Education, Culture, Sports, Science and Technology, the Ministry of Health, Labor and Welfare, and the Ministry of Economy, Trade and Industry) [7] should be carefully consulted.

6. Samples for genetic testing must be stored with utmost care. Confidentiality of personal, identifiable information as well as of individual genetic information resulting of the testing must be a top priority.
(1) As a fundamental rule, regular medical information and genetic information linked to specific individuals must be stored separately.
(2) Information regarding personal identification and individual genetic information must be kept confidential. Directing physicians, genetic counseling providers and/or any responsible officials of medical facilities should strive to prevent such information from leaking to any third party.
(3) When a part of the results of genetic testing is to be entrusted to another laboratory testing facility or institution, samples should be rendered anonymous before commission, and personal, identifiable information must be kept confidential [7, 10, 12].

7. Medical institutions or laboratory testing facilities that conduct genetic tests should provide sufficient, appropriate information to the general public to engender their understanding of the implications of genetic testing. These institutions should not conduct genetic tests for which clinical usefulness has not been established. In addition, these institutions should not advertise genetic testing [4, 12].

Ⅲ. Disclosure of Genetic Test Results

1. The rights of examinees to know or not to know test results should be equally respected.
2. When disclosing genetic test results, the wishes of examinees to have results disclosed or to refuse them should be respected. Individual genetic information gained from testing must be subject to confidentiality,

and therefore fundamentally should never be disclosed to relatives or any third party without obtaining permission from the examinees themselves. Even when the examinees agree, individual genetic test results should be protected from access by employers, health insures and schools.

3. When disclosing test results to examinees, the directing physicians should explain the results with adequate, understandable language. In the cases where the test was unsuccessful or unsubstantial for diagnosis, examinees should be so informed.
4. Those who engage in genetic testing should be constantly vigilant against the use of test results for social discrimination.
5. When the directing physicians judge that the accompanying of trusted person(s) is more suitable than the examinees alone regarding disclosure and explanation of test results, they should so recommend.
6. Test results may be disclosed to relatives with the examinees' consent. In case of refusal by examinees, disclosure to their relatives may be still possible if all the following conditions are met [see Note 5]. However, decisions for disclosure or nondisclosure in such cases should not be made on the sole judgment of the directing physician, but should be within the jurisdiction of an institutional review board (IRB, ethics committee), whose decision should be final.
   (1) When the results can be utilized as useful information for the prevention and treatment of a clinically serious disorder in relatives,
   (2) When judging that disadvantages which relatives may suffer can be prevented by the disclosure,
   (3) In cases where, even after repeated explanation to examinees, disclosure consent has not been given,
   (4) In cases where requests for disclosure have come from relatives,
   (5) When judging that examinees will not suffer discrimination, even if results are disclosed to relatives,
   (6) In cases where disclosure can lead to diagnosis, prevention and/or treatment of a particular disease in relatives,

Ⅳ. Genetic Testing and Genetic Counseling

1. Genetic testing should be carried out after adequate and thorough genetic counseling.
2. Genetic counseling should be practiced by a clinician, e.g., a clinical geneticist qualified by the Japanese Board of Medical Genetics, who is experienced in genetic counseling and has appropriate expertise in genetic medicine. Genetic counseling providers should have a good grasp of the examinees' psycho-emotional condition. Genetic counseling providers may seek cooperation from psychiatrists, clinical psychologists, genetic nurses and social workers, to work as a team.
3. Genetic counseling providers should work as hard as possible to provide accurate, most current, disease-related information to examinees. This includes information on the frequency, natural history, and recurrent risk (genetic prognosis) of the disease, as well as information on the implications of carrier detection, prenatal diagnosis and disease susceptibility tests. Genetic counseling providers should pay enough attention to heterogeneity in gene mutations, clinical manifestations, prognosis, and effects of treatments, even in the same disease.
4. During genetic counseling, genetic counseling providers are responsible for providing examinees with thoroughly understandable explanations in clear, simple language, and should confirm that examinees sufficiently understand the matters at hard. When examinees request attendance of accompanying people or when judged for its necessity, other people may be present during genetic counseling sessions.
5. The contents of genetic counseling should be recorded separately from general clinical records, and stored for a period of time.
6. At an examinees' request, following-up genetic counseling should be planned and performed to assist autonomous decision making. In addition, information about medical and social welfare services as well as clinico-psychological and social support should be provided if necessary.
7. If test results are disclosed by directing physicians to relatives (as in the case of Section III-6), the physicians should consider providing genetic counseling for the relatives and to introduce them to specialized physicians.
8. Post-test genetic counseling should also be provided, unless otherwise rejected by examinees.

Ⅴ. Important Points Concerning Genetic Testing for Specific Subjects

1. Genetic tests for persons who have developed a disease
   (1) Genetic testing may take place to establish a diagnosis.
   (2) Even in case of testing to establish a diagnosis, the directing physicians should provide adequate explanations to gain examinees' understanding that test results may consequently involve examinees' relatives.
   (3) Analysis of a disease-causing gene mutation may be carried out in patients with an established diagnosis, in order to obtain information for presymptomatic diagnosis, disease susceptibility and carrier detection of their relatives. In this case, sufficient and thorough explanation as follows should be provided before the testing: When data obtained from tests are adequately disclosed to and utilized by relatives, the genetic test will become medically meaningful; and even though a mutation is not identified, the result will not effect the clinical diagnosis of examinees.

2. Genetic Testing for Carrier Detection
   (1) When there is in a family a patient with an autosomal recessive, X-linked recessive or unbalanced chromosomal translocation, genetic testing may be carried out for carrier detection, as a test to determine whether examinees are carriers and whether the offspring may be affected with the same disorder.
   (2) In case of carrier detection, information that may be of use for future reproduction (family planning) rather than for the examinees' health-care management should be fully and adequately explained to gain clear understanding of examinees.
   (3) With a view to protecting their future autonomous decision-making, carrier detection for children should not be done.
   (4) In case of carrier detection, the directing physicians or related health care providers should be fully aware of discrimination which examinees and/or their relatives/family members may potentially suffer.

3. Genetic Testing to Predict Disorders [14, 15, 16]
   (1) Disease-predicting genetic testing includes presymptomatic testing that is almost completely predictable for the development of a single-gene disorder, and susceptibility testing that estimates the predisposition to a multifactorial disease or its risk.
   (2) Persons being subjected to disease-predicting genetic testing are generally those in good health. Therefore, strict measures to insure the protection of privacy and adequate measures for psychological support should be in place. Particular care must be taken to ensure that examinees are not discriminated against regarding admission to school, employment or taking out an insurance.

A. Presymptomatic Testing
   1) Presymptomatic testing of a disease for which an effective therapy or preventive methods are unavailable should not be performed unless the following conditions are met:
      (a) When examinees are adults capable of giving consent and themselves have requested the test,
      (b) When a gene mutation of affected person(s) within the same family has been identified, and thus, the disease can be accurately diagnosed by the testing,
      (c) When examinees have clearly understood the inheritance mode of the disorder, its clinical characteristics and detailed methodology of the test, and have a well-considered future plan in case of positive test results,
      (d) When there are medical facilities where post-onset, clinico-psychological and social support services are available, in case of positive test results,

   2) A decision to or not to perform presymptomatic testing of a disease, for which effective therapies and preventive methods are unavailable, should be made carefully under the above fulfilled conditions by physicians, including specialists for the disease, certified clinical geneticists and psychiatrists, after several occasions of genetic counseling in cooperation with clinical psychologists, genetic nurses and social workers.

B. Disease-Susceptibility Testing

1) For disease-susceptibility testing, it should have been confirmed that the sensitivity and specificity of the test as well as positive or negative predictive values are at the acceptable levels
2) For disease-susceptibility testing, the directing physicians should sufficiently explain the following points and confirm examinees' understanding [see Section II-1-(2), and Note 8]: The onset and manifestations of the disease vary even if a gene (DNA) mutation is identified; this depends on penetrance and a gene effect (contribution rate to the disease) on the susceptibility; and the development of the disease cannot absolutely be ruled out even if a mutation in the target gene is not found.

C. Genetic Testing for Familial Tumors

1) For genetic testing for familial tumors, a careful approach should be adopted, considering the existence of many diverse tumor-related genes.
2) Familial tumor susceptibility testing should follow the "Guidelines for Genetic Testing and Research on Familial Tumors and their Clinical Applications" [11] proposed by the Japanese Society for Familial Tumor, in addition to the present guidelines.
3) For familial tumor susceptibility testing, it should be confirmed that the sensitivity and specificity of the test as well as positive or negative predictive values are at the acceptable levels [see Section II-1-(2)].

4. Genetic Testing for Individual, Differential Drug Response

Diagnosis of sensitivity to drugs by testing using polymorphisms in drug-metabolizing enzyme genes may directly provide useful information for treatment. However, care must be taken that the information is not misused for discrimination, as in the case of other genetic testing.

5. Prenatal Testing and Diagnosis

(1) Prenatal testing and diagnosis in the first half of pregnancy includes cytogenetic, biochemical-genetic, molecular-genetic, and cytopathological analyses, as well as physical methods such as sonographical examination.

(2) Since genetic testing for prenatal diagnostics may involve ethical-social issues, particular care should be given to the following points:

(d) Adequate explanations and genetic counseling on the possibility (risk) of an affected fetus, diagnostic limitations of test methods, possible physical risks to the mother and fetus, and any potential side effects should precede testing to promote understanding of the couple.

(e) The testing should be carried out or directed by obstetrician(s) who have been well trained and have experience in testing and testing safety procedures.

(3) Invasive prenatal testing and diagnosis, such as chorionic villus sampling or amniocentesis in the following pregnancies should be performed only upon request from the couple who have understood the implications of the test:

(a) In cases where either parent is a carrier of a chromosomal abnormality,
(b) In cases where there is a past history of pregnancy or birth of a child with a chromosomal abnormality,
(c) In cases of pregnancy with advanced maternal age,
(d) In cases of a mother heterozygous for an X-linked disorder that presents with a severe condition in the neonatal period or in infancy,
(e) In cases where both parents are heterozygotes for an autosomal recessive disorder that presents with a severe condition in the neonatal period or in infancy,
(f) In cases where either parent is a heterozygote for an autosomal dominant disorder that presents with a severe condition in the neonatal period or in infancy,
(g) In cases where a fetus is possibly affected with a severe disorder,

(4) Except for prenatal diagnosis for a severe X-linked disorder, gender of the fetus should not be disclosed.

(5) Efforts should always be made for the quality control of prenatal diagnosis technology.

(6) When testing using so-called maternal serum markers, the following opinions should be well consulted: "Opinions Concerning Tests using Maternal Serum Markers" [17] by the Committee on Prenatal

Diagnosis, the Advanced Clinical Technology Evaluation Task Force of the Ministry of Health and Welfare; "Views on Maternal Serum Marker Testing" [18] by Bioethical Committee of Japan Society of Human Genetics; and "Opinions Concerning Maternal Serum Marker Testing" [19] by the Perinatal Committee of Japan Society of Obstetrics and Gynecology.

(7) Pre-implantation testing and diagnosis must be approached with full ethical awareness, as it is a clinical method of genetic testing still in the research stage of development and requires an extremely high level of knowledge and technology. Its practice should follow the Japan Society of Obstetrics and Gynecology's Announcement "Opinions Concerning Pre-implantation Diagnosis" [20, 21].

6. Mass-screening for Newborn Infants with Congenital Disorders

(1) Mass-screening for newborn infants is a genetic test to aim early identification of congenital disorders to allow decrease in the prevalence and mortality rates through early treatment.

(2) If newborn infants lose an opportunity to receive the screening, they may face to have disbenefit, such as an increased risk of disease development and subsequent death. Therefore, the directing physicians are recommended to make an effort to explain to the parents about the implications of the screening, and perform the screening after receiving consent from the parents (or from a surrogate). The physicians should be aware that the mass-screening is a genetic test, and provide adequate genetic counseling for parents whose infant is found and diagnosed to have a disease.

IN CONCLUSION

The Genetics-Medicine-Related Societies have established the "Guidelines for Genetic Testing". However, those who are expected to respect the guidelines may remain limited principally within the members of these societies. In other words, even if unethical, antisocial and inappropriate genetic testing is being practiced, the guidelines have no jurisdiction to regulate or prevent this kind of testing, when it is performed by people other than the society members. Therefore, we believe that in the future, as has been requested by the Japan Society for Gene Diagnosis and Therapy [22], and under the suggestion of those outside Japan, it will be necessary to establish authorized evaluation and surveillance systems for genetic testing [23]. Especially, to promote providing new information to examinees and improving the accuracy of tests, it is necessary to establish a government regulatory system for confirming sufficient levels of analytical and clinical validity and clinical utility, as well as for the assessment of quality and post-testing survey. In this way, examinees can receive medical benefits and avoid the potential suffering incurred by unwarranted, meaningless genetic tests. The absolute necessity of enforced confidentiality of individual genetic information is another important issue, calling for utmost care in application. Unless genetic testing is carried out under the aforementioned considerations, some people may refuse to be tested, because of fear of such discrimination. We finally hope that, with these guidelines as the foundation, a more effective genetic testing system based on both human rights and legislation can be established.

PROPOSALS

(1) Establishment of a government regulated system is needed to confirm that analytical and clinical validity, and clinical utility of genetic testing for a given disease are all at sufficient levels.

(2) Genetic testing facilities should be controlled under the jurisdiction of a government organization, in order to promote improvement of diagnostic accuracy, consistent handling of new genetics data, and post-test tracking by facilities.

(3) For the establishment of a comprehensive genetic medicine system including genetic counseling, training of clinical geneticists and genetic counselors by a systematic education program is absolutely necessary.

(4) Moreover, the importance of genetic medicine should be reaffirmed as a fundamental system to return the achievements and clinical applications of advanced medical research, such as genome research, to the general public. Government programs that include science-technology and health-medical-care promoting policies should be encouraged to move forward.

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Terms and Definitions

1 Susceptibility testing (test for disease susceptibility, tests for predisposing factors, testing for constitutional predisposition)

Susceptibility testing refers to predictive genetic testing for diseases where, when compared to monogenic diseases, the penetrance or the role of individual genes to the phenotype is not high (for example cancer, heart disease, and diabetes mellitus). Susceptibility testing gives a probabilistic result, so that positive result does not necessarily mean disease, and negative result not completely exclude disease. In clinical use, sensitivity, specificity, positive predictive value, negative predictive value of such tests are often problematic.

2 Genetic counseling

Genetic counseling refers to a medical activity where clinical genetic diagnosis is established for a patient with genetic disease, or for his/her family or a person who may have a disease (client), and based on the clinical genetic diagnosis appropriate information provided, such as genetic prognosis, as well as support, so that the clients may choose an appropriate course of action in the future out of their own free will. During genetic counseling, various information is exchanged based on a relationship of trust between the client and the genetic counselor to provide psychological and psychiatric support. It should be remembered that genetic counseling is not simply providing medical genetic information.

3 Genetic testing

Genetic testing is aimed at making the diagnosis of a genetic disease and involves the analysis or assays of human DNA, RNA, chromosome, protein (peptide), or metabolite. The objectives of testing include establishing definitive diagnosis, carrier testing, presymptomatic testing, susceptibility testing, pharmacogenetic testing, prenatal testing, and neonatal screening. Normally, it does not include human genomic or genetic analysis, biochemical analysis, cytopathological analysis or forensic analysis conducted purely for research purposes.

4 Genetic information

Genetic information from genetic testing includes the medical information obtained directly from genetic testing of DNA, RNA, chromosome, protein (peptide), metabolite, and family information obtained from family history that may indicate the diseases.

5 Genetic services

Genetic services refer to healthcare services devoted to medical genetics and genetic diseases. This also includes information on genetics, genetic testing, education on genetics, access to genetic counseling, and referral to patient support groups.

6 Gene

A functional unit of DNA (deoxyribonucleic acid) that codes mainly for a protein. DNA is composed of sequences of 4 nucleotide bases, adenine (A), cytosine (C), guanine (G), and thymine (T). DNA strands form hydrogen bonding between A and T, and between G and C to give a stable double-helical structure. In humans, there are 32×10^8 bases, of which about 5% are transcribed into RNA for eventual protein synthesis. Such a DNA unit is called the structural gene, and there are thought to be about 30,000 such genes.

7 Gene therapy

Gene therapy refers to a technique where a foreign gene, either as is or incorporated into a vector (a carrier), is introduced into the body to elicit the synthesis of a desired protein in the target cell or tissue for therapeutic purposes. This form of therapy is currently used for cancer therapy rather than for hereditary diseases.

8 Polymorphism

Polymorphism is defined as state of having alleles of different nucleotide sequences at a gene locus (allelic gene) that exist in multiple types and exist at a frequency of greater than 1%. These polymorphisms usually do

not directly cause hereditary diseases. Thus, with a frequency of less than 1%, mutations that cause monogenic diseases cannot be considered to be polymorphisms. Polymorphisms due to a single-nucleotide substitution (single nucleotide polymorphisms: SNPs) may be related to the risk of developing multifactorial diseases, and one current area of research involves the analysis of polymorphisms to gain a better understanding of the pathogenesis of multifactorial diseases.

9 Genetic mutation

A nucleotide base change in a gene. Base substitution (replacement of one base by another), deletion (deletion of a base), insertion (insertion of a base) or other various types of mutations may result in abnormal phenotype. Mutations can be missense mutations resulting in the replacement of one amino acid by another or nonsense mutations that cause termination of polypeptide synthesis. Genetic mutations as strictly defined indicate a direct relationship to disease, but in a broader sense might also include polymorphisms. For this reason, in the current guidelines, polymorphisms are also designated as "DNA mutations."

10 Genetic disease

Genetic diseases can be grouped generally into one of three types, monogenic diseases (Mendelian disorders), chromosomal abnormalities, and multifactorial (genetic) diseases. This includes disease-causing genetic mutations and chromosomal abnormalities passed on directly from a parent to child (inherited disease), but also situations where the parents do not have any genetic mutations but during the period of gametogenesis, a genetic mutation is formed, and the gamete with the mutation results in an individual with a genetic disease. In the latter case, this genetic mutation is not directly passed on from the parent to the child, but is a genetic disease nonetheless. The term, "familial diseases," does not necessarily refer to inherited diseases. These may include genetic diseases or diseases with exogenous factors such as infection, and teratogenic factors.

11 Genetic discrimination

This refers to discrimination of an individual or his/her family based on differences in the genome or gene from the normal genome or gene actually or predictively. Discrimination resulting from a disability caused by a gene mutation is discrimination against the handicapped and differs from genetic discrimination.

12 Karyotype

This refers to the chromosomal make-up in an individual or cell. For example, the karyotype of a normal female is 46, XX, while a male with Down's syndrome has 47, XY, +21. Karyotype is designated according to an international nomenclature (ISCN95).

13 Adverse selection

If a person applying for insurance obtains a life insurance of high value without disclosing to the insurance company of the existence of high risk of developing hereditary diseases, for example Huntington's disease, such an action may serve to decrease the fairness of the actuarial calculations. This is called adverse selection (in evolution there is a genetic term called "reverse selection," but these two terms are unrelated).

14 Prenatal testing (diagnosis)

Genetic prenatal testing (diagnosis) refers to the chromosome testing, biochemical testing, and cytological testing using chorionic villi, amniotic fluid, or amniotic fluid cells to determine the presence or absence of genetic or congenital abnormality in the fetus. In general chorionic villi are obtained at weeks 10-11 of the pregnancy, while amniotic fluid or amniotic cells are obtained at weeks 15-17 of the pregnancy. The fetal blood or fetal tissue may also be used to conduct the test.

15 Penetrance

Penetrance is the proportion of patients with a mutant gene who actually develop the disease associated with the mutant gene. Penetrance may refer to diseases with onset at birth and to age-dependent penetrance in diseases with delayed onset. The penetrance in the latter situation would be the same as the lifetime risk.

16 Germline

Cell type derived from the fertilized zygote that maintains the genotype and karyotype of the fertilized zygote. This does not include cells such as cancer cells with abnormal genotype or karyotype.

17 Bioethics

This is defined as an area of systematic research on moral and ethical aspects of life sciences and healthcare using various moral and ethical methodologies in a cross-disciplinary field (including moral perspectives, decision making, procedures, policy) (Encyclopedia of Bioethics, Georgetown University, ed.) and includes the basic principles of respect of individuals, respect of autonomy, beneficience, prevention of harm (nonmaleficience), and justice (fairness).

18 Preimplantation diagnosis

Preimplantation diagnosis refers to the technique where after a successful in vitro fertilization and progression of cleavage to three days, 1-2 cells from the embryo is harvested and subjected to chromosome testing or genetic testing, and the desired embryo is then selected and returned into the uterus of the mother for implantation (pregnancy).

19 Presymptomatic testing

For certain hereditary diseases, for example, delayed onset autosomal dominant diseases such as Huntington's disease, where the penetrance is rather high (essentially 100%), this term refers to the genetic testing conducted in healthy individuals, prior to onset of disease, who have a family history of the disease. However, one cannot make any predictions such as precise time of onset disease or severity of disease from this type of test. (See susceptibility testing)

20 Haplotype

A set of alleles located close to each other on a single homologous chromosome. Alleles located close by are often linked (linkage disequilibrium).

21 Maternal serum marker testing

A test in which serum from a pregnant woman is assayed for α-fetoprotein, free β-human chorionic gonadotropin (or total human chorionic gonadotropin), non-conjugated estriol, etc., and used along with the accurate number of weeks in gestation at the time of blood sampling to determine the likelihood that the fetus has trisomy 21 or trisomy 18. For definitive diagnosis, prenatal chromosome testing is necessary.