Regulating Preimplantation Genetic Diagnosis (PGD)

Regulating Preimplantation Genetic Diagnosis—How to Control PGD

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Purpose: To assess the regulations for Preimplantation Genetic Diagnosis (PGD). How to regulate and control PGD. Is any special licensing procedure necessary?

Methods: A review of the statements of the organization and the Japan Society of Obstetrics and Gynecology (JSOG). Also, we assess the JSOG guidelines for PGD and the statements on diagnosis of genetic diseases of the Japan Society of Human Genetics. We discuss extra licenses and qualifications for laboratories, staff, and directors.

Results: At present, there are no regulations governing PGD for laboratories, scientists, directors, and staff. Regulations are set by committees and organizations of the countries involved. We don't have any worldwide system of controls. In Japan, we are considering regulations in the fields of reproduction and genetics.

Conclusions: PGD requires high-level techniques in taking samples, and high-level knowledge about genetic diseases. In diagnosis, we have to be as close to 100% accurate as possible. However, samples for PGD are so small that there is always a risk of failure. Also, we are required to have highly specialized knowledge about reproduction and genetics. In Japan, JSOG has a plan to join with the Society for Investigating Infertility and Society for Genetics.

KEY WORDS: Embryo biopsy; polymerase chain reaction (PCR); preimplantation genetic diagnosis (PGD); preimplantation genetic diagnosis-aneuploidy screening (PGD-AS).

INTRODUCTION

Preimplantation genetic diagnosis (PGD) is a prenatal diagnostic method involving biopsy of a specimen from an embryo in utero undertaken prior to implantation. Medical institutions adopting this technique have been increasing worldwide (in a general trend) since a report of sexuality diagnosis by Handyside *et al.* in 1990 (1). In recent years Munné *et al.* introduced preimplantation genetic diagnosis-aneuploidy screening (PGD-AS), which the group of investigators applied to evaluation of embryos (2). The objectives of PGD are broadly divided into genetic diagnosis and evaluation of quality of the embryo. The

ESHRE PGD Steering Committee examined a total of 1,318 gravidisms at twenty-five institutions between 1977 and December 2000 (3). The basis for the worldwide increase of PGD cases, needless to say, consists in improvement in biopsy techniques and the advent of single-cell PCR and fluorescence in situ hybridization (FISH) (4,5). PGD is no doubt an integration of in vitro fertilization-embryo transfer (IVF-ET), microscopic embryo manipulations, and molecular-biological techniques. It thus requires highly specialized, advanced techniques; yet, high levels of safety in embryo manipulations and a high correct genetic diagnosis rate must always be maintained. Couples desiring PGD should be provided with a full explanation of the procedure, safety, and diagnosis rate beforehand. Further, elaborate systems including post-PGD counseling must be developed. In many countries at present, including Japan, technical safety and ethical problems are still at issue regarding PGD, so it has not

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Table I. JSOG Guidelines

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- a. PGD is a highly advanced medical technique and is performed as a clinical research activity.
 - b. The operator should be a physician who has mastered advanced knowledge and techniques regarding reproductive medicine, and should be versed in hereditary disorders and thoroughly experienced in prenatal diagnosis.
 - c. The medical institution where PGD is carried out must have experienced cases of delivery via in vitro fertilization-embryo transfer and possess positive achievements in prenatal diagnosis.
 - d. This diagnostic procedure should be applied only to serious hereditary disorders.
 - e. The person/institution intending to perform PGD should file an application with the Society using a prescribed application form and obtain approval from the Society.
 - f. Only mutually consenting couples with a strong desire for the examination should be approved to receive PGD.
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been introduced into clinical practice as yet. We have explored control and regulatory systems that would be needed for implementation of this prenatal diagnostic approach by review of the systems currently in use at institutions and countries that have adopted the technique and countries considering adopting the technique. More concretely, the Japan Society of Obstetrics and Gynecology (JSOG) and the Japan Society of Human Genetics (JSHG) guidelines and the literature on PGD served as references. This paper deals with discussions about institutions where PGD is performed, the head of the institution, operators, supervisory facilities, and relevant potential problems.

MATERIALS AND METHODS

The JSOG guidelines for PGD and the JSHG guidelines for genetic diagnosis are presented below with expositions (Tables I, II, III and IV).

Present Status of Preimplantation Diagnosis in Japan (JSOG's View) (6)

While the guidelines prescribe the above, PGD has not yet been applied clinically. Further, target

disorders for the diagnosis are limited to hereditary diseases.

JSHG Guidelines for Genetic Diagnosis and DNA Diagnosis, and Program of Certification System

The JSHG has evolved a licensing system for medical genetics specialists and has formulated a pertinent training program (8).

RESULTS

Is There a Need for Extra License(s)?

There is no country where a particular license is required for physicians to conduct PGD at present. A movement is advancing here in Japan towards future requirements for authorization by the JSOG (10) or the Japan Society of Fertility and Sterility (JSFS) of physicians if one wishes to perform assisted reproductive techniques (ART). Furthermore, the JSHG has started a certification system for medical genetics specialists and counselors. No particular certification system exists for PGD yet, however.

Table II. Disorders Subject to DNA Diagnosis

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1. Serious sex-linked recessive hereditary disorders
 - (1) Duchenne's muscular dystrophy
 - (2) Lesh-Nyhan syndrome
 - (3) Hunter's disease
 - (4) Hypogammaglobulinemia (Bruton's)
 - (5) Haemophilia A & B
 2. Current indications for chorionic villus sampling (CVS) in Japan
 - (1) Either parent being a carrier of chromosomal aberration
 - (2) A history of previous delivery of a child with chromosomal aberration
 - (3) Advanced maternal age
 - (4) A carrier of a serious X-linked recessive hereditary disease
 - (5) A carrier of a serious inborn error of metabolism that can be diagnosed by fetal diagnosis
 - (6) A carrier of a serious hereditary disorder that can be diagnosed by DNA diagnosis
 - (7) Others
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Table III. JSHG Guidelines for Genetic Diagnosis (7)

Hereditary disorders diagnosable by human DNA probes (a process hereafter referred to as genetic diagnosis) have been increasing yearly, and the clinical usefulness of genetic diagnosis has become widely recognized. On the other hand, sensitive issues have arisen, such as the need for pre- and postgenetic diagnosis hereditary counseling, handling of personal genetic information gained via the diagnosis, and biologic specimens used in the diagnosis. Genetic diagnosis is undertaken not only to confirm a diagnosis in a patient with an overt disease but also, based on the information obtained, to screen the patient's family members and clients without signs/symptoms of hereditary disease for carrier states, as well as to provide presymptomatic diagnostic detection and prenatal diagnosis. By genetic diagnosis, it may be feasible to directly detect a mutant gene etiologically responsible for a disease or, utilizing DNA polymorphism, to indirectly determine with a fairly high probability whether the mutant gene is present or not. An appropriate diagnostic procedure is selected for conducting the genetic diagnosis depending upon the target disorder, genetic information, biologic specimens collected, and so on. The JSHG hereby proposes that, in the practice of genetic diagnoses for hereditary disorders, the human rights of the person to receive the diagnosis, hereafter referred to as the subject, and his/her family members should be protected, that a proper spread of genetic diagnosis be promoted, and that the Japan Society of Human Genetics "Guidelines for Counseling on Hereditary Problems and Prenatal Diagnosis" proposed in December 1994 be observed, with the following matters being noted.

1. Even the same hereditary disease often manifests diverse genetic mutations, clinical pictures, prognoses, and therapeutic responses. This should be taken into careful account in conducting genetic diagnosis for hereditary disorders.
2. At pregenetic diagnosis counseling, the counselor must supply exact information to the subject on the objectives, procedures, and precision of genetic diagnosis and, especially, diagnostic limits that cannot be avoided, besides routine counseling on hereditary problems. To eliminate omissions, it is desirable that the explanation be not only verbal but also provided by means of a document for each disorder.
3. Before genetic diagnosis, informed consent must be obtained from the subject. The client and his/her family members have the right to be informed as well as to reject information (right to be uninformed/right to be reluctant to know), and both should be respected. As for presymptomatic diagnostic detection of adult-affecting inborn error in particular, pre-diagnosis counseling should be repeated and it should be confirmed that the decision-making is based on the self-discipline of the subject him-/herself. In such instances, it is advisable that the decision be made in the presence of two or more counselors.
4. In a case where the subject is judged to be incompetent to make a decision independently and his/her proxy are to make the decision, the decision must be such that it protects the rights of the subject.
5. The physician may refuse a request from a client for genetic diagnosis if he/she cannot agree with the request in the light of social and/or ethical norms, or according to his/her principles.
6. Genetic diagnosis must be performed with procedural completeness and technical skill. Examinations at two or more different laboratories may be considered to ensure accuracy. Institutions where the examination is carried out must always strive to improve diagnostic precision and should be placed under definite precision control, including postdiagnosis follow-up.
7. The results of the diagnosis should be judged by a number of experts with adequate knowledge of gene analysis who are also well versed in the target disorders.
8. The results of the diagnosis should be explained to the subject in plain language. The explanation should include disease prognosis, clarifying the relationship of the mutant gene with the disease state among other factors. Even if the diagnosis has been unsuccessful or results of the diagnosis are inaccurate, the nature thereof must be clearly explained to the subject.
9. In explaining a diagnostic outcome, the counselor should advise the subject that it might be preferable to have someone he/she trusts sit in attendance. A subject receiving diagnostic examination may request that it be discontinued even before its completion, and refuse to be informed of any diagnostic outcome.
10. Postdiagnosis counseling is essential and, when deemed to be necessary, should be continued periodically.
11. Personal information secured by gene analysis should be administered and controlled confidentially, by the person directly involved in the counseling, and must not be conveyed to any other person than the subject. In a case where the subject is judged to be incompetent, so that the genetic diagnosis is made on the decision of his/her proxy, the diagnostic outcome should be conveyed only to the said proxy.

However, confidentiality may be relinquished as necessary in cases where the subject has agreed to this, or in cases where, even if the subject has not given consent, conveyance of the information would enable prevention of serious damage which a specific person might otherwise sustain, and such a deed is judged to be reasonably necessary. Nevertheless, such a decision should not be made by the counselor but rather at the discretion of a relevant ethical committee or the equivalent.

12. Specimens that have been used in genetic diagnosis may be preserved for the benefit of the subject and his/her family. Specimens must not be used for any purpose other than genetic diagnosis. Personal information on specimens is subject to confidentiality. If it is judged that there is any possibility of future use of the specimen for diagnosis of related disorders, it must be clearly explained to the subject that the specimen will be provided upon deletion of information specifying the individual subject and, separately, the subject's consent should be obtained in writing.

Laboratories

Medical institutions where ART are performed have an obligation to register themselves with a registration form designated by the JSOG (11). Each such institution must report annually to the said Society the outcomes including number of cases in which ART was undertaken, pregnancy rate, and fertility rate.

Whilst PGD is not performed currently in Japan, it is a matter of course that, in other countries, the number of cases examined by PGD and the outcomes are to be included in the items reportable to ART-registered institutions accredited for the technique.

The director of such an institution, needless to say, must have advanced knowledge and mastery of techniques in reproduction, and should be well-versed

Table IV. JSHG Program for Specialty Certification System (9)**1. Role of clinical genetics specialist**

Clinical genetics specialists, as clinical specialists for hereditary disorders, assume a role in preserving and promoting the health of the patient and his/her family members and in early detection, prevention and treatment of a disorder, medical care, and education/consultation through grasping the hereditary disease patient as a whole person and as a member of a family and local community. They are expected to contribute to the promotion of the health and development of the welfare of the nation via clinical genetic research and clinical practice of medicine for hereditary disorders.

2. The image of an ideal clinical genetics specialist**(1) Self-discipline**

The physician as a clinical genetics specialist should constantly and actively pursue his studies/practice, and endeavor to absorb knowledge relevant to the latest medical care/medicine/medical genetics information about hereditary disorders and clinicogenetic techniques, to make accurate diagnoses of hereditary disorders, and to foster the ability to select the most appropriate measures and treatment. The physician should also strive to accept objective evaluations by others.

(2) Ethics of medicine

The clinical genetics specialist should accomplish his/her duties on the grounds of his/her social and professional responsibilities as a physician and on the grounds of the ethics of medicine. In view of the disease being a hereditary disorder, furthermore, the physician should fully respect the patient's and patient's family members' human rights, right to be informed of and right to be reluctant to know, and respect their privacy. The patient's voluntary decision-making should be respected. The physician should listen with attention to the various opinions of the patient, other physicians, and the community, seek the judgement of the ethics committee, etc., and accomplish his/her duties in accordance with the Medical Service Law and the Medical Practitioners Law.

(3) Attitude toward patient and family members

The basic attitude toward the patient and his/her family members should be to win and keep their trust, to provide sufficient explanations, and to obtain their informed consent. A sincere attitude and psychological support are imperative especially toward a patient bearing an inborn error causative of lethal or permanent disability and his/her family members.

(4) Explanation to the patient and family members

The patient and his/her family members should be provided with adequate explanations, suited to their individual backgrounds, as to the clinical manifestations of the hereditary disorder, and the pathogenetic mechanism, pathophysiology, natural history, clinical progress, prognosis, and treatments thereof. If deemed necessary, an explanation based on medical genetic facts may be given. The physician should understand the significance of patient organizations and patient support organizations and positively cooperate with them.

(5) Cooperation with other healthcare professionals

Medical care may be carried out in cooperation with physicians and healthcare professionals from other fields of medical specialization and other medical institutions. In those instances, the clinical genetics specialist shall provide the attending physician with appropriate advice from the standpoint of clinical genetics. The clinical genetics specialist should fully understand and render cooperation in regard to the education/training and qualifications of healthcare professionals other than physicians.

(6) Community medical care

The clinical genetics specialist may participate in and contribute to domestic and foreign community plans regarding health preservation and medical care for hereditary disorders. The clinical genetics specialist may take charge of education in clinical genetics for other healthcare professionals engaged in community medical care.

(7) Making good use of medical care and social resources, and mediceconomics

The clinical genetics specialist should understand and make adequate use of laws, cabinet orders and ordinances related to medical care/welfare, medical insurance policies, and the payment-at-public-expenses system. Particularly in the case of a disabled or chronically-ill patient, the clinical genetics specialist may perform appropriate management and guidance so that the patient can enjoy daily living as much as possible, through cooperation with medical and healthcare organizations such as regional medical associations and public health centers, welfare-related organizations such as public welfare offices and child guidance centers, day-care centers, rehabilitation centers, vocational training centers, and schools. The clinical genetics specialist should understand the expenses involved in medical practice and the cost-benefit relationships, and recognize the relationship between improvements in medical care and the economy.

(8) Clinical genetics research

The clinical genetics specialist him-/herself should pursue clinical genetics studies or collaborate in other research in order to contribute to advances in medical genetics.

3. General medical care capabilities**(1) Taking down the patient's medical history and family history, and recording the medical history**

The clinical genetics specialist should be able to take down such items in the medical history and family history of the patient that are of value to the diagnosis, measures for and treatment of hereditary disorder, and should be able to make problem-oriented medical records.

(2) Medical examination

The clinical genetics specialist should be capable of performing medical treatment with proper techniques/procedures and of appropriate description and summarization of the treatment. The clinical genetics specialist should always be able to make a comprehensive observation of the whole body system.

(3) Diagnosis

The clinical genetics specialist should be capable of accurately grasping problems existent in the patient, selecting necessary examinations/laboratory tests based on the medical history, family history, and findings on medical examinations, and making an appropriate diagnosis through integration of the information gained. The clinical genetics specialist should be able to refer the patient to other specialists on the grounds of the findings in the medical examinations and tests.

Table IV. (Continued)

(4) Measures to be taken, treatment, medical care, patient education/guidance, and prevention	The clinical genetics specialist should be competent to choose the most appropriate treatment, supporting and preventive measures, with consideration for individual situation/peculiarities in the patient's family, from among the many conceivable measures available to cope with hereditary diseases or inheritance-related disorders.
(5) Concern about familial genetic predispositions and diseases	The clinical genetics specialist should be capable of early detection, prevention, and treatment of individuals with the same genetic predisposition or disorder as the proband within the same family.
(6) Hereditary problem counseling	The clinical genetics specialist should be able to conduct appropriate counseling on hereditary problems for the patient and his/her family.
(7) Consideration of social living and rehabilitation	The clinical genetics specialist should be attentive, so that patients with disorders may be rehabilitated and participate in social activities with the minimal, if any, missing out on the opportunities of life, and may incur no interference with school attendance or employment.

in genetics. It is stipulated that those who conduct genetic diagnoses are desirably physicians with a board-certified specialist's diploma. The staff should be composed of physicians, an embryologist, a medical genetics specialist, and a counselor.

Quality Control Processes

Research laboratory environment should be managed and controlled by a PGD committee of experts composed of members from the JSOG, JSHG, and JSFS, in order to maintain the best possible status constantly. The facility should be maintained as independent and exclusive for PGD to sustain the quality of PGD. Likewise, instruments must be exclusively for use in the diagnosis.

Reporting

Request forms for PGD, reports of PGD, and informed consent forms should be submitted to the committee. Reporting must be made to the above-mentioned PGD committee monthly, encompassing the number of cases examined, purpose of the diagnosis, techniques used and results (including photographic records). It is preferable that an informed consent form signed by the patient and spouse be appended to these documents. Examples of written information for the patient and an informed consent form are presented in Tables V and VI.

DISCUSSION

Medical institutions where PGD is conducted and the number of cases examined by this procedure have been increasing worldwide. However, there are no established regulations for such institutions and op-

erators as yet, nor have any internationally common views been endorsed. PGD is grossly divided into genetic diagnosis and PGD-AS that evaluates the quality of the embryo. Whatever the diagnostic approach, PGD is a practice that should be permitted only to those who are profoundly knowledgeable about and have technical skill in both ART and molecular biology. Needless to say, therefore, regulations for conduct cannot materialize without participation by the Society of Human Genetics as well as the Society of Obstetrics and Gynecology and the Society of Fertility and Sterility (12). Joint meetings of reproductive medical care specialists and medical genetics specialists are now actively convened in Japan in view of prospective PGD implementation (13). Qualifications for a PGD specialist may come into being in the future. At present, the reproductive medical care specialist should perform PGD-AS for the purpose of assessing embryonic quality and the aims of genetic diagnosis should be left to the medical genetics specialist. The director of a medical institution where PGD is undertaken should be a reproductive medical care specialist with advanced knowledge about PGD. Therefore, a program to provide at least a minimum acquisition of knowledge and techniques in PGD must be incorporated as part of the current training for reproductive medical care specialists. A certification system for physicians who conduct genetic diagnoses based on PGD should be established at the academic society or national level. Also, a PGD expert committee should be set up so that frequent inspections may be made of environmental control at PGD facilities. Such facilities should always be reviewed on the grounds of the number of cases examined and the success rate. We have made an attempt to explore regulations for PGD by reviewing reports to domestic academic societies and the literature on PGD. PGD is a union of the most advanced techniques in reproduction and genetics.

Table V. Written Information on PGD for the Patient

Prior to conducting preimplantation genetic diagnosis, it is important to obtain informed consent from the patient upon having given a full explanation of the merits and demerits of the procedure.

1. Details of the explanation

The explanation should be given in detail along with a specifically written document regarding the following fourteen items.

- (1) What is the preimplantation genetic diagnosis for a fertilized egg?
- (2) Sex-linked recessive hereditary disorders
- (3) Procedure of preimplantation genetic diagnosis
- (4) In vitro fertilization
 - 1) Procedures for in vitro fertilization-embryo transfer, 2) pregnancy rate, and 3) complications associated with in vitro fertilization
- (5) Precision of genetic diagnosis
- (6) Safety of amniotic fluid examination, cord blood test, and chorionic villus examination
- (7) Screening for XY-spermatozoa by density gradient centrifugation on Parcoll
- (8) Handling of the fertilized ovum diagnosed as male type by sexuality diagnosis
- (9) Handling of fertilized eggs that are aneuploid, undiagnosable, or surplus
- (10) Premature termination of preimplantation genetic diagnosis procedures
- (11) Status of infants born by preimplantation genetic diagnosis procedures in Europe or the United States
- (12) Follow-up at this department of infants born by preimplantation genetic diagnosis procedures
- (13) Confidentiality and disclosure of information
- (14) Expenses for preimplantation genetic diagnosis procedures

Table VI. Informed Consent Form for PGD

INFORMED CONSENT FORM: PREIMPLANTATION GENETIC DIAGNOSIS FOR FERTILIZED OVUM (EXAMPLE)

To: Director of the Hospital

We have been fully informed of the procedure noted above, preimplantation genetic diagnosis, with the appended written explanation, at our sincere desire. We hereby agree as to the following matters.

1. We recognize that the preimplantation genetic diagnosis essentially involves in vitro fertilization. We have been given a full explanation of the pregnancy rate by and potential complications of in vitro fertilization at present, to which we have assented.
2. We agree to transfer of a fertilized ovum of which sexuality has been diagnosed as female as well as to cryopreservation, in principle, of a fertilized ovum of which sexuality has been diagnosed as male.
Furthermore, we also consent to cryopreservation of a fertilized ovum which has been diagnosed as sex chromosome aneuploidy or undiagnosable; nevertheless, we will decide on another occasion whether such cryopreservation be done or not at our desire.
3. We have come to know that the precision of sexuality diagnosis for fertilized ova is about 90%. Therefore, we agree to receive a chorionic villus test, cord blood test, or amniotic fluid test to reconfirm the sexuality of the ovum once pregnancy has been established after the preimplantation genetic diagnosis.
We, the couple, will ultimately decide whether to proceed to parturition or not in this instance.
4. We have heard that preimplantation genetic diagnosis was initiated in the United Kingdom in 1989 and that there has been no case of birth defect that is attributable to this diagnostic procedure to date, yet we recognize that the procedure is still a new diagnostic approach.

Subject's Signature

Date

Subject's Spouse

Date

We have fully explained to the couple above the nature and purpose of preimplantation genetic diagnosis at the sincere desire of the couple for pregnancy and delivery upon receiving preimplantation genetic diagnosis of a fertilized ovum. We have given a full explanation of the procedure with its possible benefits and risks using appended written information to obtain informed consent from the couple desiring preimplantation genetic diagnosis, and we are convinced that the couple have fully understood the explanation.

[Subject's Outpatient Medical Char No. _____]

Informant Physician's Signature

Date

Informant Physician's Signature

Date

Department of Obstetrics and Gynecology
Faculty of Medicine
XXX University Hospital

Specialists in the respective realms of science must take part in that union. A particular set of requirements are needed for physicians to perform genetic diagnosis based on PGD in the narrow sense of the term, although the certification seems not to be a requisite for all physicians who conduct PGD (if one includes PGD-AS) for the time being.

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