Regulating Preimplantation Genetic Diagnosis (PGD)

What Regulations for Preimplantation Genetic Diagnosis?

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Purpose: To discuss the qualifications of personnel involved in either (a) embryo biopsy/slide fixation, (b) performance of preimplantation genetic diagnosis-specific assays, or (c) interpretation of findings and results from such studies.

Methods: Illustrate similarities and differences between the qualifications and licensing requirements for personnel involved in high complexity testing in other laboratory specialties, such as microbiology or endocrinology.

Results: Parallels can in fact be drawn between specific personnel certification and licensing requirements for reporting test results following preimplantation genetic testing and those for other clinical specimens submitted for testing.

Conclusions: Assisted reproductive technology programs generally do not have personnel certified in cytotechnology or clinical genetics. Programs that perform the actual interpretation of specimens submitted for evaluation by fluorescent in situ hybridization will have to have supervisory personnel certified to perform such interpretations to ensure the level of quality control and assurance now afforded in centers for assisted reproductive technology.

KEY WORDS: Licensure; preimplantation genetic testing; qualifications.

Preimplantation genetic testing and diagnosis of human cleavage stage embryos is a multistep, multidisciplinary challenge to ART laboratories. Like so many other advances in ART, PGD came about by adapting techniques developed in animal model systems and human research materials before clinical application was attempted. PGD has followed the same path as other “watershed” advances in ART (IVF, cryopreservation, assisted hatching, ICSI, TESE) in that ART clinics began to apply them clinically ahead of bona fide, double-blinded, controlled randomized studies proving them to be safe and efficacious.

There is a fundamental difference, however, between PGD and these other procedures, and that is in the reporting of findings or results from the PGD studies that are used to make therapeutic decisions. It is this inherent quality of PGD work that places it

in the same category as a semen analysis—they are both reports on clinical findings from high complexity tests that are used by clinicians to direct therapy. California and New York, as examples, require laboratories reporting tests, and the personnel performing them to have state certification and licensure allowing them to do so. Arguments continue to this day about whether clinical laboratory standards should apply to ART procedures and reports as well as whom should have deemed status to inspect and administrate the licensing process.

The field of ART has since its inception filled technical as well as laboratory director positions with persons competent in basic biological laboratory skills. *Academic qualifications* have been broadly defined as having to have a bachelor's degree in the biological sciences for technical positions, and higher for supervisory ones. A few years ago the American Board of Bioanalysts began offering certifying examinations for personnel either working in or directing ART laboratories. This was a step in the direction of developing a standard for persons in these positions.

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Cytotechnologists or medical laboratory technologists require certification and licensure, and I believe the same will become true for persons analyzing and reporting the findings from PGD, as it is an analogous endeavor. The true question is what type of academic or prior work experience qualifies someone to apply for certification/licensure to perform PGD analyses, and moreover, which analytical techniques are currently considered licensable?

About 90% of PGD being performed today is for aneuploidy—the rest of the cases are usually to evaluate the presence of either translocations or gene defects. Aneuploidy (and many translocations, it appears) is evaluated using fluorescent in situ hybridization, or FISH, of a selected panel of chromosome specific probes. Up to nine chromosomes (including the sex chromosomes) are typically evaluated on biopsied blastomere nuclei for aneuploidy cases. Translocations require acquiring specific whole chromosome painting probes, and testing them on peripheral blood lymphocytes from the patient-couple prior to ovulation induction to be sure a good evaluation can be made. The quality of the results from FISH on fixed nuclei is dependent on how well that step was performed, and further, the selected blastomere for removal must contain a nucleus. A skilled embryologist must be the person to perform the embryo biopsy, but beyond that, other trained personnel could perform the slide fixation of blastomere nuclei (an unwieldy arrangement, but possible) and even a third type of specialist could perform the actual FISH assay on these materials. Deciding therefore on what constitutes appropriate qualifications and certification of personnel who are involved in this work can become quite complex, and this does not even consider the qualifications required of the laboratory director.

At the time of this writing, most if not all, ART laboratory directors in U.S.-based programs have sat for a specific exam administered by the American Board of Bioanalysts, the purpose of which is to certify the directors as being competent to oversee a laboratory engaged in “high complexity testing” as defined by the College of American Pathologists. These exams are specifically tailored to specialty laboratories such as endocrine, microbiology, cytogenetics, and now ART. This means a certified ART lab director is not qualified to oversee, for example, a microbiology laboratory. This clearly can present a problem for ART clinics that perform the FISH component and reporting of results for PGD cases. Someone certified in cytogenetics should be the named supervisor for at least this portion of the services offered by such a clinic.

QUALITY CONTROL

The quality control/quality assurance mechanisms as applied currently to U.S.-ART clinics could be adapted to include PGD services, just as these mechanisms were adapted from other licensed laboratories to ART clinics. Adherence to manufacturer's guidelines for use, storage, and shelf life of the reagents involved in the performance of FISH assays, for example, is similar to what is done in the ART laboratory itself, with accurate record keeping reflecting routine monitoring and maintenance of hardware associated with the performance of FISH.

REPORTING REQUIREMENTS

I believe an opportunity exists at this early stage of expansion of PGD services to develop a standardized reporting format of the FISH results. ART clinics have not been required to do this, and as a result every one of the over 400 known ART clinics have their own version of a summary of laboratory findings. This presents problems when patients switch ART clinics, and their records follow them to the new clinic, the staff of which then must do their utmost to interpret what happened in the previous ART cycles. The Society for Assisted Reproductive Technology, a branch of the American Society for Reproductive Medicine, failed to give this idea the attention it deserved over a decade ago, and therefore standardization of lab summaries as well as semen analyses reports, endocrine reports, and others never got sufficient traction to become requirements. Standardization of FISH reports can reduce the possibility of misinterpretation of their contents, and everyone charged with the responsibility of reading them would benefit.

CONCLUSIONS

PGD is an emergent technology used to investigate at a molecular level the characteristics of early human embryos. Its use will only grow as more and more applications are delineated through research into this extraordinary field. At this time, standardization of qualifications for facilities, equipment, personnel, and methods of quality control/quality assurance have not been formalized. Because of the multidisciplinary nature of PGD, several different types of personnel, and indeed laboratories may become involved in a single case of PGD, much of it occurring outside the ART program itself in most cases. Qualifications of

personnel who directly interpret FISH results should probably be established along those developed for licensed cytogeneticists who interpret FISH-treated cytogenetic specimens.

Fixation of the nuclei of biopsied blastomeres should be performed by embryologists, as it is they who are most familiar with working with these types of materials. As with other micromanipulative procedures that have become commonplace in ART clinics (assisted hatching, ICSI), proficiency can only come

with practice. Most ART clinics have materials left over from ART cycles such as triploid zygotes, arrested cleavage stage embryos that with patients permission could be used to gain fluency with the techniques of biopsy/slide fixation. Standards of how to best proceed with these processes will come soon enough, and it should be an extension of the responsibilities of persons qualified to be embryologists rather than an entirely separate technical subspecialty with ART.