Chapter 25
Regulatory Aspects of Embryo Testing: An American View

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Introduction

For decades, the high incidence of multiple gestation in the practice of assisted reproductive medicine has been of concern to infertility physicians and regulators alike [1]. The interface between government regulation and medical practice has brought varied responses to bear on this problem. One initiative is the move toward single embryo transfer (SET) in IVF, which is now recommended by physicians' groups and mandated by some governments. Within this initiative, the quest to find the best method of identifying the euploid embryo, the chromosomally normal embryo with the best chance of leading to a healthy pregnancy and healthy offspring, is ongoing [2, 3].

Preimplantation genetic screening (PGS) and preimplantation genetic diagnosis (PGD) are terms often discussed together to designate tests that help clinicians and their patients select the proper embryo to transfer toward the conclusion of an IVF cycle. Although the techniques used are similar, the objectives of PGS and PGD are distinct. Through PGS, doctors aim to identify euploid embryos so that a pregnancy can be achieved and maintained [4]. PGD contemplates screening embryos for specific genetic markers, either to select against embryos possessing anomalies that cause disease in favor of embryos possessing certain nonmedical traits like gender [5]. Thus, whereas PGS is indicated primarily for couples who struggle to become pregnant or who suffer recurrent pregnancy loss, PGD is appropriate for both infertile and fertile couples.

Unlike in other countries where SET is mandated, there has been less movement in this direction in the United States [1]. The high cost of infertility care in this country and the lack of insurance coverage for it create anxiety among patients

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E Scott Sills (ed.), *Screening the Single Euploid Embryo*,
DOI 10.1007/978-3-319-16892-0_25

whose motivation toward maximizing the chances of pregnancy conflicts with values inherent in the move to SET [6]. The doctor and the patient may thus find themselves at odds [1]. In the current environment, it behooves medical professionals conducting PGS and PGD to be familiar with the legal and other regulatory dimensions of their practice area.

Methods

This investigation employed a systematic review of published sources on law, bioethics, and reproductive health policy.

Results

The key sources of regulation impacting on the practice of the genetic testing of embryos in infertility clinics include the US Constitution, statutes and administrative regulations, medical malpractice law, and professional norms. Beyond rules that prohibit discrimination, that guarantee the privacy of patient information, and that govern molecular genetic testing in laboratories and the qualifications of genetic counselors, little in the Constitution, statutes, or administrative regulations bears directly on PGS and PGD. This leaves medical malpractice law and the norms of professional societies as the primary regulatory mechanisms that define the standard of care and the requirements of informed consent in embryo testing for IVF. Fertility societies may wish to bring their influence to bear on legislative initiatives to regulate insurance coverage for IVF so that the movement toward SET may be more fully realized.

Discussion

In a classification of the regulation of embryo testing as liberal, prohibitive, or cautious, the United States might well rank as "laissez-faire," a classification reserved for countries with almost no regulation whatsoever [7]. That virtually no federal law or regulation directly addresses embryo testing in infertility care may partly be a function of the fact that legislative competence in the area of medical practice currently lies with the states by virtue of the Tenth Amendment to the United States Constitution. The lack of regulation at the state level as well may have to do with the battle over abortion that continues to rage in this country. Since the regulation of IVF and related practices invariably triggers questions of the status of the embryo, politicians are loathe to grapple with this issue for fear of alienating certain constituencies.

The Constitutional Overlay

The US Constitution acts as a brake on legislation and other state action that impinges on the procreative liberty of individual citizens. Procreative liberty is a negative right guaranteeing against governmental interference in the exercise of procreative aims but not guaranteeing any assistance toward the accomplishment of those aims. Although commentators often posit that restrictions on access to assisted reproduction raise ethical issues of procreative autonomy [8], whether procreative liberty subsumes resort to assisted reproduction as a legal matter remains an academic question. The federal courts have made only a very few discrete pronouncements on the matter [9, 10]. For example, a lower court has held that chorionic villi sampling within the first trimester of pregnancy, falls within the ambit of constitutionally protected procreative freedom, since it is designed to provide information relevant to keeping or terminating a pregnancy [10]. Because PGS and PGD provide information relevant to commencing a pregnancy, they, too, might fall within the protected ambit. Restrictions on them would therefore likely be constitutionally infirm, but a more solid prediction is difficult to make. The issue is, moreover, unlikely to arise with any frequency in a system where so little regulation exists.

For clinics engaged in embryo testing for IVF, the relevance of the Constitution's guarantee of procreative liberty will become clearer if the issue of embryo testing ever reaches the US Supreme Court. The Court could easily draw a distinction between PGS, the aim of which is successful procreation, and PGD, whose aim is the selection of an offspring's traits. The Court might be of the opinion that procreative liberty does not extend to PGD. Moreover, the Court might decide that the line should be drawn between embryo testing and prenatal testing, with the latter on the side of procreative liberty because it implicates a pregnant woman's bodily integrity. A very conservative Court could well determine that neither prenatal testing nor embryo testing are exercises of procreative liberty.

Whether a clinic would ever have to defend itself against a patient's claim of procreative liberty is doubtful. Most infertility clinics in the United States are private entities. Their activities thus do not constitute the state action that is a prerequisite for a valid constitutional claim. Where a clinic is an arm of the state, as where it is a unit within a public university, the Constitution does apply to its actions. But being a public facility in no way means that a clinic is bound to provide any particular service. The most viable constitutional claim in such a context would be one alleging class-based discrimination in the delivery of care. Even then, a clinic may escape liability if the targeted group is not one that receives the highest level of protection in the litigation of individual constitutional rights. At present, regulations that treat individuals differently based on matters of race and ethnicity receive the highest level of judicial scrutiny in constitutional rights cases. Discrimination against other groups, though, may be prohibited by statutes that apply to both public and private facilities (see section "Statutes and Administrative Regulations," below).

For any legislation to be a proper exercise of governmental power, it must promote public health, safety, welfare, or morals and utilize means that are at least rationally related to those goals. To satisfy the Constitution, though, legislation must not be so

vague as to leave unclear what conduct it prohibits. Infertility physicians in Illinois raised vagueness in their challenge of a prohibition on nontherapeutic fetal experimentation [10]. The court agreed that the statute failed to define "experimentation" and "therapeutic" and so left unclear whether it prohibited the physicians' use of evolving prenatal diagnostic techniques. With respect to embryos, statutes in other states contain similar prohibitions on experimentation, but most of these appear to address research on embryos [11]. Since PGS and PGD for IVF are not research experiments and are perhaps routine enough not to be considered experimental [12], these statutes arguably do not apply to these techniques.

Statutes and Administrative Regulations: Privacy, Safety, and Equality

Statutes and administrative regulations are codified rules enacted by legislatures and the agencies to which they delegate rulemaking authority. At the federal level, Congress often delegates rulemaking power when special expertise is required to implement the provisions of a statute. Administrative agencies thus become "arms of Congress" and must act consistently with their statutory mandate.

Very little in either American statutes or administrative regulations bears directly on embryo testing for IVF. Nonetheless, there are several provisions of which clinicians should be aware. These provisions aim to promote privacy and safety in matters of genetic testing and to combat the discrimination that might occur were sensitive genetic information to fall into the wrong hands.

The Centers for Disease Control (CDC) and the Food and Drug Administration (FDA), divisions of the US Department of Health and Human Services, are tasked with protecting the United States from health, safety, and security threats and regulating biological products for human use, respectively. The CDC's regulation of assisted reproduction lies in its implementation of the Fertility Clinic Success Rate and Certification Act. This statute requires clinics that provide IVF services to make annual reports of their success rates to the federal government. These reporting requirements do not include information about the use of or results achieved from PGD [13].

The FDA specifically regulates "human cells or tissues intended for implantation," [14] a category that includes oocytes and semen. The FDA's specific goals are "to ensure that donors do not harbor infections that could be transmitted to recipients" [15] and to minimize the risk of contamination in the handling of human tissues. The governing rules require establishments that handle human cells and tissue to register with the FDA and require screening and testing of tissue donors "for risk factors for, and clinical evidence of, relevant communicable disease agents or diseases" [16]. The necessary screening does not, however, require genetic testing of tissue donors (Anderson H., US FDA 2014, personal communication). The testing requirement also does not extend to "[r]eproductive cells or tissue donated by a sexual intimate partner of the recipient for reproductive use" [17]. The FDA sometimes inspects establishments for compliance with these rules. The FDA also regulates medical devices, such as products used to perform genetic tests [18]. Whether

the FDA is competent to regulate the genetic testing techniques developed by genetics laboratories in-house has been the subject of debate in recent years. The FDA has, however, issued a set of nonbinding recommendations for the regulation of laboratory-developed genetic tests in some cases [19]. Once a medical device is approved by the FDA, the actual use of it by physicians does not fall within the purview of its regulatory authority.

The Clinical Laboratory Improvement Amendments (CLIA) aim to ensure the quality of laboratory testing through a certification program. The program is administered by the Centers for Medicare & Medicaid Services, another division of the US Department of Health and Human Services. The Amendments apply to laboratories that conduct assays on human bodily material in the course of medical treatment. Laboratories that conduct genetic testing must meet the basic criteria for labs performing high complexity tests generally. To enhance this oversight, the CDC has promulgated a set of good laboratory practices in molecular genetic testing for heritable diseases and conditions (good laboratory practices in biochemical genetic testing are the subject of a separate CDC publication). The practices address the qualifications of laboratory personnel, the testing process, and the privacy of patients' information, among other things, but do not explicitly refer to the genetic testing of embryos for transfer [20].

At the state level, there is virtually no direct regulation of PGD, except for laboratory quality assurance programs requiring laboratories performing PGD to acquire a permit [21–23]. Under New York's Clinical Laboratory Evaluation Program, which regulates laboratories performing PGD on specimens originating in New York, a laboratory must "obtain the subject's informed consent and include in their reports a statement of and an interpretation of its findings, the test's technical limitations, suggestions for additional testing, recommendations for referral to a genetic counselor (if applicable), the test methodology, and a list of all variants examined in the assay" [24]. Although a waiver procedure is available, New York's permit requirement has produced anxiety among clinics that the limited number of permitted labs capable of providing specialized assessment of embryos and the tight turnaround time required for IVF will impact negatively on patients [25]. Currently 18 laboratories in New York State and 59 outside of New York have permits to perform molecular genetic testing. Not all of these laboratories, though, offer PGD.

Genetic counseling has also been of interest to state regulators in recent years. Several states require genetic counselors to be licensed, often in conjunction with the certification programs established by the American Board of Genetic Counseling or the American Board of Medical Genetics [26]. These licensing schemes do not in all cases apply to licensed physicians who provide genetic counseling [27] but also may not permit physicians to call themselves genetic counselors without procuring a license [28].

The Health Insurance Portability and Accountability Act (HIPAA) provides minimum standards for ensuring the confidentiality of patients' health-care information. Under HIPAA, laboratories that conduct molecular genetic testing must take steps to "ensure the confidentiality of patient information, including molecular testing information and test results" [29]. Some states have similar privacy laws that explicitly apply to genetic testing and define genetic information as protected health

information [30] or as the property of the individual to whom the genetic information relates [31]. These laws limit the ways in which health professionals may use what they uncover in the course of examining embryos destined for IVF. Civil and criminal liability attaches to the violation of genetic privacy laws [32].

Finally, discrimination in matters of genetic testing is forbidden by statute. The federal Genetic Information Nondiscrimination Act (GINA) [33] and analogous state laws prohibit health insurance carriers and employers from discriminating against individuals based on their genetic information. The drafters of GINA were concerned that discrimination could occur against healthy individuals based solely on their genetic predisposition toward certain diseases. The statute's implementing regulations explicitly include preimplantation genetic diagnosis on embryos created using IVF within the definition of a genetic test [34], and "[g]enetic information" includes "genetic information of any embryo… " [35].

It is difficult to imagine a cognizable claim of discrimination being brought against infertility physicians under this enactment based on the use of information disclosed by PGS or PGD. First of all, to constitute a discriminatory act under GINA, the selection would have to be based on genetic information and not simply on morphology. More importantly, GINA was passed to combat discrimination in the workplace and in the issuance of health insurance. The Act does not implicate differentiating between embryos in the clinic in pursuit of SET, because the selection and de-selection of embryos for this purpose do not relate to employment or to the issuance of health insurance.

Unlike GINA, there are other antidiscrimination provisions that do relate directly to the conduct of clinics. Oklahoma's Freedom of Conscience Act, for example, prohibits employers from discriminating against personnel who refuse for religious reasons to perform a "medical procedure on an in vitro human embryo that is not related to the beneficial treatment of the in vitro human embryo" [36]. Whether this provision relates to the selection and de-selection of embryos via PGS or PGD remains unclear. State statutes prohibiting discrimination in public accommodations also apply to clinics. These statutes do not compel clinics to offer embryo testing services, but the refusal to serve a patient in a specific case because of the patient's sexual orientation or marital status is illegal in some states. A doctor's religious objection would likely be inadequate to defend against a charge of protected class-based discrimination in the provision of care [37]. Any discrimination in the delivery of care would most likely occur well before the point of embryo testing; nonetheless, clinics that offer PGS and PGD will need to be aware of state and local antidiscrimination laws when making determinations about which patients they will allow to receive these services.

Medical Malpractice

Medical malpractice is a type of tort liability applicable where injury to a patient is caused by a physician's failure to discharge a duty of care toward that patient or the physician fails to obtain a patient's informed consent to treatment. Liability for

medical malpractice in the United States is determined by courts deciding individual cases and is remedied by awards of money damages. Without question, with growing scientific understanding of human genetics and the perfection of new diagnostic tools, medical malpractice liability in the genetic screening and testing realm is expanding [38].

Courts have traditionally deferred to professional custom to define physicians' duties of care. Some states have enacted statutes codifying this deferential stance; [39] others have enacted statutes and administrative regulations that define the standard of care for certain practice settings [40] or that specify the elements of informed consent for certain procedures [41]. In the field of reproductive medicine, courts lacking legislative guidance would be likely to take into account standards of care established by physicians' societies like the American Society for Reproductive Medicine (ASRM) (see section "Professional Norms," below). Indeed, some statutes defining the standard of care refer explicitly to the Society's standards [42]. Despite this development, there is no truly uniform standard of care for the practice of infertility medicine in the United States [43].

In the context of preconception or preimplantation screening, medical malpractice liability has been imposed primarily in cases where the harm at issue arose from the negligent screening of gametes or negligent preimplantation counseling [44]. For example, in one case, the clinic knew the egg donor was a carrier of cystic fibrosis but did not undertake to ascertain whether the biological father was also a carrier of the disease [45]. The intended parents alleged that the clinic had been negligent in its preconception and preimplantation counseling and had deprived them of informed consent. Such claims may be dismissed if they are used to disguise what it is essentially a claim of wrongful life brought on behalf of the child. The legal theory of wrongful life is that one may recover damages against a physician if it would have been better not to have been born at all [46]. Whereas courts may reject such claims as better suited to resolution by philosophers or theologians, similar facts have supported claims of wrongful birth, under which parents seek to recover for the cost of raising a disabled child [45].

A recent study documented medical malpractice claims arising from negligently performed PGD [47]. The authors surveyed lawsuits brought against clinics based on theories of negligence as well as those brought based on a failure to obtain informed consent. Within this latter group were allegations that the patients were not told of the particular clinic's inexperience with PGD, to what extent PGD can be error-prone, or even that PGD was an option. Such cases do not specify exactly what physicians should tell patients about PGD. But they do counsel that, at the very least, patients should understand the many uncertainties of PGD, including that the smaller number of embryos available for implantation following PGD makes "pregnancy expectation following PGD somewhat less than for IVF in general" [48]. Likewise, patients agreeing to PGS should know of its limitations, particularly within certain patient populations. For either PGD or PGS, patients should understand that it is unknown whether the biopsy itself might be a source of harm, even though at the present time experts are doubtful [49]. The practice guidelines of the ASRM would be quite useful to clinics interested in developing an informed consent protocol (see section "Professional Norms," below).

The clinician offering PGS and PGD must not only be capable of explaining to patients the goals and techniques of these procedures, but, in the case of PGD, of detecting genetic disorders so as to counsel patients appropriately. This specific duty in the context of PGD is an extension of the general duty of an obstetrician to be "alert to the detection of genetic disorders or other conditions in the patient that could lead to birth defects" [50]. Indeed, the typical factual predicate in cases where liability is imposed for negligently performed PGD is also that a child has been born with a disorder that a properly performed PGD would have disclosed. Negligently performed PGS, however, would normally result in no pregnancy at all, a risk infertility patients already assume given the current state of the technology of IVF. It is thus difficult to see how PGS could result in malpractice liability, unless negligent handling of the embryos resulted in their being rendered unsuitable for transfer at all [51].

Professional Norms

As made clear above, most aspects of infertility clinics' practice are not governmentally regulated in the United States. A majority of clinics oppose governmental regulation but do not resist regulation from within the profession [52]. As such, voluntary professional organizations play an important role in the oversight of PGD [53].

The self-regulation of reproductive medicine physicians consists of a certification offered by the American Board of Obstetrics and Gynecology or the American Board of Urology and membership in the American Society for Reproductive Medicine (ASRM). It is estimated that over 95% of infertility clinics in the United States are members of the Society for Assisted Reproductive Technology (SART). A clinic's membership in SART is made contingent upon its adherence to ASRM's guidelines and minimum standards, the qualifications of its staff, accreditation of its reproductive laboratories, and its reporting of its success rates to the CDC [54, 58]. There are no legal consequences for physicians or clinics that elect not to be members of ASRM or SART, but of course consumers may prefer clinics that are members to those that are not.

The ASRM's practice guidelines relating to PGD are aimed at the treatment of couples at risk for conceiving a child with a genetic disease or other abnormality. They recommend counseling about the risks of extended culture and embryo biopsy and the risk of misdiagnosis in PGD, which may lead to the "transfer of an affected embryo thought to be normal or the discard of a normal embryo thought to be affected" [55]. The opinion recognizes that both PGD and PGS can be used to exclude embryos unsuitable for transfer, but with respect to PGS specifically recommends counseling patients that a false positive result "may lead to the discard of a normal embryo" and that a false negative result "may lead to the transfer of an abnormal embryo." These guidelines would be relevant in a malpractice action (discussed above) to establish the standard of care with respect to the state of the science and to define the scope of the duty to inform. Indeed, they were specifically raised by the plaintiffs in a case that later settled before trial for $1.3 million [45].

Apart from its practice guidelines, ASRM has issued a body of ethical pronouncements intended to advise clinics. As a part of this ethics initiative, the ASRM has issued two guidelines related to the genetic testing of embryos, one addressing sex selection and the other the detection of adult-onset diseases. Although ASRM believes that sex selection for the purposes of disease prevention is ethical, it rejects using PGD for sex selection for nonmedical reasons [56]. As long as sperm-sorting techniques are safe and parents "affirm that they will fully accept children of the opposite sex if the preconception gender selection fails," ASRM does approve of preconception sex selection for family balancing or for first children, because it imposes fewer burdens on embryos and parents [57].

ASRM has recognized IVF with PGD as "a major scientific advance" over post-conception diagnosis and pregnancy termination [55]. Of using PGD to screen for adult-onset diseases, ASRM makes a distinction between serious and less serious adult-onset conditions. It concludes that PGD is ethically justified in cases of serious conditions where interventions for the conditions are nonexistent, ineffective, or burdensome. PGD is also justified in cases of lesser severity as long as PGD is a low-risk procedure [59]. The Committee urges the participation of an experienced genetic counselor to assist patients considering PGD.

Although it is thought that "most practitioners follow [ASRM's ethical] guidelines," the guidelines themselves are in the nature of standards for self-regulation only [52, 54]. A lack of downward pressure on clinics from either the legal system or the primary professional association with regard to these may mean that some IVF clinics do not deliver PGS and PGD in precisely the way ASRM advises. Both the practice guidelines and the ethics pronouncements contain, however, important reminders that clinics, whether or not members of a professional society, must fully inform patients about the risks of any procedures performed so that they may make considered judgments about how to proceed. This advice to clinics, if not heeded, could have legal consequences (see section "Malpractice," above).

Insurance

Financial limitations on the ability of patients to afford PGS or PGD have been identified as barriers to the acceptance of SET as the norm in infertility clinics. At the same time, studies have concluded that IVF with PGD can be highly cost-effective in comparison with prenatal diagnosis and pregnancy termination or the cost of raising a sick child [60, 61]. This research is transferable to the context of PGS for SET, it being well known, for instance, that the high incidence of multiple gestation in assisted reproduction is costly not only for individuals but for society at large [1]. For this reason, ASRM believes that broader insurance coverage of assisted reproduction "could promote the most medically appropriate procedures and reduce the incidence of multiple births with their accompanying risks and costs" [62]. This transformation would occur from two directions. If insured, patients who could otherwise afford fewer rounds of IVF would not be as driven toward the

transfer of multiple embryos; insurers on the other side of the equation would likely require that providers adhere to ASRM's guidelines, as is already true in a handful of states. With patients, physicians, and insurers on the same page, more progress could be made toward establishing SET as a professional norm.

The lack of public insurance for IVF in the United States contrasts sharply with what by comparison in other countries seem to be lavish public subsidies. Public funds, like those available under New York's Infertility Demonstration Program, are rarely available, and most states, unfortunately, do not mandate that private insurers cover or offer to cover infertility care. Of those that do, the statutes vary considerably. Some even exclude IVF, suggesting a lack of coverage for PGS and PGD, which require IVF and may also be considered insufficiently proven therapies. One restriction common to insurance mandates is that coverage extends only to heterosexual couples who have medically diagnosed infertility. Such a mandate would appear to exclude PGD for couples who are not technically infertile. Thus, mandated insurance coverage for PGS and PGD remains largely out of reach [63].

Where insurers do cover IVF, they are likely for some time to come to resist covering PGS and PGD as "experimental" or as not "medically necessary." However, the good news is that some patients holding policies covering expenses related to infertility, genetic counseling, and prenatal testing have challenged such resistance and won coverage for PGD. Although couples who need PGD are not necessarily infertile, the argument that PGD is nonetheless "medically necessary" is particularly compelling in cases where the intended parents are carriers of genes that cause disease, and the insurer will otherwise be responsible for covering the costs of the child's medical care [48]. Furthermore, as the techniques for conducting PGS and PGD become further refined through research and clinical practice, insurers will have less of a basis for objecting to them as experimental. Such a development would bring PGS and PGD further into the mainstream, with salutary effects on the regularization of the use of SET in infertility clinics.

Conclusion

Few regulatory barriers currently stand in the way of clinicians practicing PGS and PGD in the United States. In a 2008 survey of clinics, nearly half of the clinics surveyed strongly agreed that "there will be restrictions on using PGD for nonmedical genetic traits such as sex" [53]. To date, though, there has been no regulatory movement in this direction. Legislative efforts to curb prenatal sex determination and selection have targeted sex-selective abortion in particular [64]. Statutes that circumscribe experimentation on embryos are aimed at research, not at clinical applications. Finally, on the professional side, ASRM has held a firm ethical stance against PGD for sex selection for over 15 years. The concerns expressed in the survey that enforceable restrictions on PGD for sex selection are on the horizon appear to be unfounded.

As Justice Michael Kirby put it in another context, "in the regulation of technology, events rarely, if ever, stand still" [65]. Philosophical positions abound about technological developments in the life sciences, but the translation to regulation must weather the political process. Legislative inaction is often the result, especially where the group that would be most affected by regulation has a powerful enough role in its formulation to advance "self-regulation as a strategy of influencing and possibly preventing future state intervention" [66]. Kirby may as well have been writing about assisted reproduction in the United States, where developments in embryo screening technology have inspired a decidedly minimalist legislative response, but where the profession has been active in promulgating practical and ethical standards for its use in the clinic. Despite this dominance of professional control of embryo testing for IVF, whether SET will become the standard for clinical practice is doubtful in the absence of stronger mandates for funding PGS and PGD. The current state of affairs suggests that medical malpractice law will have the most direct influence on the clinical use of embryo testing for the foreseeable future.

Conflict of Interest The author reports no conflict of interest.

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