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Regulating Preimplantation Genetic Testing across the World: A Comparison of International Policy and Ethical Perspectives

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Preimplantation genetic testing (PGT) is a reproductive technology that, in the course of in vitro fertilization (IVF), allows prospective parents to select their future offspring based on genetic characteristics. PGT could be seen as an exercise of reproductive liberty, thus potentially raising significant socioethical and legal controversy. In this review, we examine—from a comparative perspective—variations in policy approaches to the regulation of PGT. We draw on a sample of 19 countries (Australia, Austria, Belgium, Brazil, Canada, China, France, Germany, India, Israel, Italy, Japan, Mexico, Netherlands, Singapore, South Korea, Switzerland, United Kingdom, and the United States) to provide a global landscape of the spectrum of policy and legislative approaches (e.g., restrictive to permissive, public vs. private models). We also explore central socioethical and policy issues and contentious applications, including permissibility criteria (e.g., medical necessity), nonmedical sex selection, and reproductive tourism. Finally, we further outline genetic counseling requirements across policy approaches.

Preimplantation genetic testing (PGT) is an assisted reproductive technology (ART) that, in the course of in vitro fertilization (IVF), enables the practitioner to select embryos by genotype prior to transfer to the womb (Knoppers et al. 2006; French Republic rev. 2019). Although IVF was originally developed to assist couples who were infertile or unable to conceive naturally, advances in PGT allow fertile individuals or couples to undergo IVF in order to conceive a child who does not have a genetic condition for which they would otherwise be at risk (e.g., because one prospective parent is affected or a carrier). PGT can also be used to conduct human leukocyte antigen (HLA) matching, in order to select for a child that is an HLA match for an existing sibling, a concept commonly referred to as a "savior child" (Kakourou et al. 2017). An HLA-matched child can then serve as a hematopoietic stem cell donor for a sibling affected by a disease such as leukemia. However, in theory, PGT can be used to select

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for any genetically determined characteristic desired by the parents, including sex and certain physical characteristics.

In 1967, scientists used fluorescence microscopy to identify the sex of living rabbit blastocysts, setting the path for the development of the technology that would later become PGT (Edwards and Gardner 1967). Clinical application of PGT would only follow in 1990, in the case of two couples who were at risk for adrenoleukodystrophy and X-linked intellectual disability (Handyside et al. 1990). In these cases, U.K. physicians used single-cell biopsies from embryos followed by Y chromosome–specific DNA amplification to select for female embryos, which would be unaffected by these X-linked conditions. Since then, techniques such as polymerase chain reaction (PCR) and fluorescent in situ hybridization (FISH) have been used to identify embryos carrying an expanding range of genetic conditions with increasing accuracy (Harper and Sengupta 2012; Van der Aa et al. 2013). Advances in sequencing and interpretation methods have further increased the possibilities provided by PGT, including using rapid embryo genotyping in combination with parental genome sequencing to predict the whole genome of an embryo, a step that would allow us to identify most Mendelian disorders, as well as some well-defined complex diseases (Kumar et al. 2015). Alongside these technical advances, there has been an "ever-increasing" number of PGT cycles performed, for a constantly increasing number of indications (Harper et al. 2012) as observed by the European Society of Human Reproduction and Embryology (ESHRE).

The possibilities provided by PGT have subjected the technology to significant legal, ethical, and social controversy since it was first developed. The "specter of eugenics" looms large, as the world grapples with the legacy of past eugenic practices (e.g., United States, Canada, and Germany) and the implications of a technology that enables selection of offspring according to preference for specific characteristics (Bayefsky 2016) without a medical indication. Similarly present in the PGT discussion, as with other forms of ART, are concerns regarding interference with the natural processes of reproduction. Although PGT allows individuals or couples to avoid the issue of choosing to terminate a pregnancy that is posed by postimplantation prenatal diagnostic techniques, issues of moral status and personhood of the embryo still play a significant role (Baertschi 2008). Additionally, the tension between individual reproductive autonomy and the interest of the state in regulating reproduction runs throughout the discussion.

Because of these socioethical concerns, the use of PGT is the subject of many laws and international policies. In this review, we will analyze the regulation of PGT across a diverse sample of jurisdictions and policy approaches, covering a continuum from restrictive to permissive policy models. Based on this continuum, we selected as an illustrative sample the following 19 countries: Australia, Austria, Belgium, Brazil, Canada, China, France, Germany, India, Israel, Italy, Japan, Mexico, Netherlands, Singapore, South Korea, Switzerland, United Kingdom, and the United States. For each country, we identified the normative and legislative documents that govern the use of PGT. In addition, we identified international regulations set forth by regional regulatory bodies, such as the Council of Europe, as they complement the national policy framework in multiple countries in our sample. In the first section, we examine these norms in terms of their regulatory approaches (public or private ordering) and degree of permissibility (restrictiveness on the use of PGT). We also discuss the implications of recent changes in regulations. In the second section, we identify and discuss several central issues present in these regulations (or consequences thereof), including criteria for permissibility, nonmedical sex selection, genetic counseling requirements, and reproductive tourism.

THE REGULATORY LANDSCAPE

In this section, we analyze the regulation of PGT in 19 countries, according to their regulatory approaches and degree of permissiveness. The laws and regulations referenced in this section can be found in the supplementary material (see Supplemental Table S1 online).

Regulatory Approaches

A country's approach to regulating PGT can be categorized in several ways. Countries may approach regulation through public ordering (top-down, state-led), private ordering (bottom-up self-regulatory approach), or a mixture of the two models (Table 1; Knoppers and Isasi 2004). In a public ordering approach, the use of PGT is governed by statute or legislation. These statues may vary widely in their criteria for acceptable use, from establishing blanket prohibitions to restricting the application of PGT to limited indications. Conversely, a private ordering approach instead relies on guidelines or self-regulation. As with public ordering, these approaches range in degree of permissiveness. Additionally, regulations governing PGT fall on a spectrum frequently characterized by the binary distinction between "soft" and "hard" laws or policies, based on the degree to which a policy is legally binding or enforceable. Although recognizing the practical benefits of such categorization, it is important to note that "soft" and "hard" laws often act as mutually reinforcing or complementary policy instruments, thus rendering any binary classification as arbitrary.

A "soft" policy is not legally binding and thus is observed only through voluntary compliance by physicians and other practitioners. This includes guidelines or position statements from professional organizations such as the American Society for Reproductive Medicine (ASRM), which suggest best practices but have limited coercive powers as they often do not carry sanctions or entail consequences for failure to comply. However, professional guidelines can positively contribute to complementing a policy framework as they often detail clinical practice, determining what constitutes the "standard of care." Another benefit of this type of "soft" policy is that guidelines are easier to update than legislative mandates and thereby are faster to respond to scientific and social developments (Simpson et al. 2006). In contrast, a "hard" law or policy carries binding, legally enforceable obligations, which may be enforced by a coercive body such as a court or licensing authority and which carry sanctions as a consequence for failure to comply. Depending on a given framework, such policies impose penalties ranging from criminal sanctions to pecuniary fines and to professional or licensing suspensions or even debarment. One example of such a policy is India's *Pre-conception and Prenatal Diagnostic Techniques (Prohibition of Sex Selection) Act*, which outlines consequences, for both patient and practitioner, for the use of PGT to determine the sex of an embryo (Republic of India 1994 rev. 2003; Tribune News Service 2017; Kumar and Sinha 2018). A first offense by a practitioner "shall be punishable with imprisonment for a term which may extend to three years and with fine which may extend to ten thousand rupees," while the patient who sought the use of PGT may receive "imprisonment for a term which may extend to three years and with fine which may extend to fifty thousand rupees." (The reasons for this policy regarding sex selection, as well as its limitations, are discussed in a later section.) "Hard" policies may be issued by both national legislative bodies as well as by professional organizations, if granted the ability to place sanctions on members. One such example is Brazil's Federal Medical Council (CFM), which has the constitutionally granted power of applying sanctions for violations to the Code of Medical Ethics (Federal Medical Council 2010). Although CFM does not have the power to pass legislation regarding PGT (no such legislation exists in Brazil), it does

Table 1. Regulatory frameworks by country

Legislative	Guidelines	No identifiable regulation
Austria	Australia	Mexico
Belgium	Brazil	
Canada	China (mix model)	
France	Israel	
Germany	Japan	
India	Singapore	
Italy	United States	
Netherlands		
South Korea		
Switzerland		
United Kingdom		

have the ability to adopt resolutions regarding ethical conduct of physicians, as it did for PGT with, for instance, the *Resolution CFM No. 2.013/2013*, which enforced sanctions on those physicians who were found in violation of the ethical code (Federal Medical Council 2013).

Countries with government-sponsored health care (such as France, Italy, and the United Kingdom) adopt a public ordering approach to regulate if and how PGT is covered by government funding, though this approach is not exclusive to countries with such programs (Bayefsky 2016). National and professional organizations may still weigh in on the practice of PGT through policy statements and guidelines, which may serve to fill in the gaps left by vague or outdated legislation. For example, although Canadian federal law regulates the use of ART, including PGT, on a broad level, organizations such as the Society of Obstetricians and Gynaecologists of Canada (SOGC) provide more detailed guidelines governing the medical practice of PGT, thus defining the contours of what constitute the standard of care at a given time (Canada 2004 rev. 2012; Dahdouh et al. 2015). In this way, public and private ordering as well as "soft" and "hard" policy work together to form the regulatory landscape in which PGT is practiced.

In some countries, regulatory approaches to PGT differ based on their political structure, such as between those at the state and federal level. Although Australia has only guidelines at the national level, at least three states have enacted legislation regulating PGT. In the United States, regulation of PGT would similarly fall to individual states; however, no state currently has laws regulating the use of PGT. This split jurisdiction can sometimes result in conflict, such as when Canada passed a 2004 federal law regulating assisted human reproduction (AHR), which included provisions relating to PGT. Much of this law was struck down in 2010, for overstepping provincial authority (Supreme Court of Canada 2010; Snow 2018). Although the ruling significantly reduced federal regulatory power, certain prohibitions were left in place, including prohibitions relevant to PGT. The province of Québec, meanwhile, introduced several laws and guidelines of its own to regulate PGT (Québec 2010).

Degree of Permissiveness

Within each regulatory approach, control of PGT may range from complete prohibition to the placement of moderate to strict restrictions. Across the globe, no country has adopted policy conferring absolute or unfettered access, yet policy vacuums, legal loopholes, and/or ineffective oversight have resulted in some jurisdictions adopting a de facto laissez faire approach.

Permissive approaches toward use of technologies such as PGT may arise from differing underlying values. A permissive approach may be adopted "with the belief that it is beneficial for humanity" or as a result of a consumerist approach to regulation that values self-enforcement (Isasi et al. 2016). A mix of both approaches appears to be at play in the regulation of PGT. Among the countries examined, the most permissive approaches to PGT can be found in the United States and Mexico. In both countries, which each follow a private ordering model, PGT is actively practiced and commercially available, including for nonmedical sex selection (Dondorp et al. 2013). In the United States, multiple professional societies have published policy statements or guidelines offering recommendations regarding the practice of PGT. The Society for Assisted Reproductive Technology (SART) and the ASRM describe PGT as "a major scientific advance" for parents at risk of passing a "heritable and debilitating genetic disease" to their children, indicating a belief in the beneficial nature of the technology (SART, ASRM 2008).These guidelines are generally supportive of the use of PGT, although varying in opinion on such issues as sex selection and medical necessity. However, lacking enforcement provisions, the degree to which the recommendations set forth in these guidelines are followed is up to the discretion of the provider, in line with the consumerist approach. In Mexico, very little regulation exists related to PGT. It has been stated that in Mexico "there are no rules," because the federal *General Health Law* does not specifically regulate any form of assisted reproduction (Mexico 1984 rev. 2018; Palacios-González and Medina-Arellano 2017). Whereas the *Regulations of the General Health Law on Health*

Research do address research related to assisted reproduction, these regulations do not relate to routine clinical practice of PGT (Mexico 1986 rev. 2014).

It is worth noting that although Japan takes a similar private ordering approach, PGT has not been as quickly or widely adopted there as in the United States or Mexico. PGT was practiced actively in the United States by 1994 and Mexico by at least 2001 (Handyside 1994; Jones and Cohen 2001). Although clinical PGT research was approved in Japan in 1998, as late as 2004, PGT had never been implemented (Sato et al. 2015). This is in large part because of the reluctance of the Japan Society of Obstetrics and Gynecology (JSOG), which requires members abiding by its guidelines to seek approval for PGT from its ethics committee, and which feared approving of discrimination toward persons with genetic conditions (Munné and Cohen 2004). Despite the lack of legal restrictions, these professional guidelines seem to carry more moral weight than those of professional organizations in the United States, effectively prohibiting the use of PGT through reluctance to approve individual cases. However, approval and subsequent use of the technique is now steadily increasing, demonstrating a shift in acceptance of PGT from research to common practice (Sato et al. 2015).

The remaining 16 countries in our sample place some degree of restriction on the use of PGT. These restrictions may take the form of substantive requirements, regulating which patients and conditions qualify for PGT, or procedural safeguards, regulating the process by which PGT is provided (Knoppers and Isasi 2004). Procedural requirements often serve to protect patient's rights, including requirements for informed consent from couples or an individual undergoing PGT or legislative mandates for the use of genetic counseling (as found in several countries including Germany, Switzerland, and France). Procedural requirements may also concern the civil status of the patient and oversight for the use of PGT, such as the requirement that PGT be performed only in specifically licensed centers. Substantive requirements, meanwhile, address the way in which PGT may be used, within the procedural framework. Substantive requirements might include the requirement for "medical necessity" as a component of eligibility for PGT, and more restrictive countries further limit the use of PGT to only such inheritable conditions deemed suitably "serious" or "severe." The prohibition of nonmedical sex selection (Table 2) is another common substantive requirement. These restrictions, which will be addressed at length later in this review, serve to ensure safe medical practices and to limit the practice of PGT to only those situations deemed ethically and morally sound by that country's cultural and regulatory standards.

Table 2. Regulation of nonmedical sex selection by country

Nonmedical Sex Selection			
Legislatively prohibited	Prohibited by guidelines	Allowed (limited circumstances)	Allowed/not regulated
Australia	China	Israel	Mexico
Austria	Brazil		United States
Belgium	Japan		
Canada	Singapore		
France			
Germany			
India			
Italy			
Netherlands			
South Korea			
Switzerland			
United Kingdom			

A Changing Landscape

No countries identified in this analysis have prohibitive regulations on PGT currently in force. This reflects a recent transformation, as over the past decade changes in national regulation have demonstrated an increasing acceptance of PGT. As previously described, PGT has seen increasing uptake in countries such as Japan, which had previously been reluctant to endorse the practice. Germany, Switzerland, and Austria had previously been singled out as having among the most prohibitive stances toward PGT (Knoppers et al. 2006; IFFS Surveillance 07 2007; Jones and Cohen 2007). Each of these countries has since implemented legislation explicitly permitting PGT, albeit under heavy restriction. This shift toward permissiveness reflects changing cultural attitudes, broader adoption of PGT in clinical practice, and judicial interest in the right to reproductive freedom.

National and international courts have played a role in the shift toward permissiveness. The legislative shift in Germany was predicated by a 2010 German Federal Supreme Court decision acquitting a Berlin physician of violating the prohibitive 1990 *Embryo Protection Act* (EPA), finding that there are some cases in which PGT may be permissible (Federal Republic of Germany 1990 rev. 2011; Turner 2011). Prior to this ruling, the EPA had commonly been interpreted to prohibit PGT because of its strict prohibition of the production and use of a human embryo for any purpose other than inducing a pregnancy (or preservation for future use). The 2010 ruling may reflect a shift away from the legislative and cultural view of PGT as a tool for selecting *against* unwanted embryos, toward a view of PGT as a means to select *for* healthy embryos, with the end goal of inducing a "healthy" pregnancy (Bock von Wülfingen 2016). Following this ruling, the German Parliament voted to approve a 2011 amendment to the EPA explicitly addressing PGT, allowing the use of PGT in select cases, including risk of "serious hereditary disease."

In Italy, a series of court rulings challenged the 2004 *Rules on Medically Assisted Procreation*, which, under the strict interpretation initially followed, restricted access to ART and outright prohibited the use of PGT (Italian Republic 2004; Turillazzi et al. 2015). The law restricted the use of medically assisted reproduction to cases in which no other method exists to "remove the causes of sterility or infertility" and limited the production of embryos to only the number "absolutely necessary," capped at three. In addition, the law prohibited experimentation on embryos, including "to predetermine genetic characteristics" except for "diagnostic and therapeutic purposes which are exclusively associated with it for the protection of health and development of the embryo itself." Although Italian courts legitimated the use of PGT to prevent serious genetic disease, access to ART (including PGT) remained restricted to infertile heterosexual couples (Turillazzi et al. 2015). In 2012, the European Court of Human rights ruled in favor of a fertile Italian couple seeking access to PGT, finding the Italian law to be in violation of the "right to respect for his private and family life" provided by the Convention for the Protection of Human Rights and Fundamental Freedoms (Council of Europe 1950; *Costa and Pavan v. Italy*, ECHR 2012).

At the permissive end of the spectrum, particularly in the United States, there appears to be a shift of focus from *if* to *how* PGT should be used. Most guidelines released by U.S. professional organizations in recent years begin with the assumption that PGT is an accepted and increasingly useful technique in reproductive medicine (ASRM 2017). These newer guidelines, rather than addressing the acceptability of the broad practice of PGT, focus on specific ethically contentious scenarios such as the transfer of embryos with genetic conditions or testing for adult-onset conditions.

REGULATION OF GENETIC COUNSELING AND KEY ISSUES IN THE PRACTICE OF PGT

In this section, we discuss several specific issues within PGT regulation, including the role of genetic counseling in PGT, as well as key issues such as nonmedical sex selection, medical necessity, and reproductive tourism.

Regulation of Genetic Counseling

Genetic counseling can play a key role in supporting potential parents in decisions related to PGT. Several countries have taken steps to require specific counseling regarding genetic conditions. This counseling may be provided either by a professional genetic counselor (in countries where such a profession exists) or by the physician providing treatment (including in countries that do not have an independent genetic counseling profession). These regulations typically specify what information must be provided during the process of obtaining PGT, although the exact persons or methods for providing that information are often unspecified. Germany, for example, does not have a genetic counseling profession, but requires that a woman seeking PGT be informed and advised "on the medical, psychological and social consequences of the genetic examination of embryonic cells" prior to providing consent for the procedure (Federal Republic of Germany 1990 rev. 2011). In Switzerland, the *Reproductive Medicine Act* requires undergoing counseling before any ART technique can be used, followed by a period of reflection before treatment. In addition, the act requires that "comprehensive genetic counseling must be provided to couples if assisted reproductive techniques" such as PGT "are used to avoid the transmission of a serious, incurable disease" (Swiss Confederation 1998, revised 2017).

Specific information to be provided at these counseling sessions is outlined within the law or respective guideline, including the risks and benefits of testing, as well as resources and information regarding specific conditions. In the United Kingdom, the Human Fertilization and Embryo Authority (HFEA) code of practice requires centers offering PGT to ensure that patients are provided with access to genetic counselors before and after treatment (HFEA 2019). However, in reference to prenatal testing, French law requires that a pregnant woman be referred to a "multidisciplinary center of prenatal diagnosis" if there is a "definite risk" of a condition, in order to receive further information (French Republic rev. 2019).

Although requirements for genetic counseling ensure that patients have access to accurate information regarding PGT and the conditions being tested for, some requirements may have the effect (intended or not) of discouraging patients from using PGT or pursuing certain actions (such as abortion) upon receiving the results. Although the United States does not require genetic counseling for all uses of PGT, federal law and statutes in a number of states require the provision of specific information following a prenatal diagnosis of Down syndrome or "other prenatally … diagnosed conditions" (United States 2008). Advocates argue that these laws ensure patients receive accurate information regarding the lives of persons with Down syndrome (or other conditions), whereas critics of these laws suggest that legislatively regulating the information provided to patients in this manner violates the ethical norm of "strict neutrality" in genetic counseling (Caplan 2015). In either case, it is generally understood that the goal of this legislation is to influence the patient's decision-making following prenatal testing, with the goal to reduce the number of patients choosing to terminate their pregnancy after receiving a prenatal diagnosis (Reilly 2009). In this case, PGT may be seen as a better alternative to prenatal screening (PNS), in which testing is conducted during pregnancy, as it avoids the need to make a choice to have an abortion if a genetic condition is identified. However, PGT still raises the question of whether selecting against conditions such as Down syndrome is discriminatory toward persons with disabilities, who live fulfilling lives in spite of their medical conditions. This discussion is playing out beyond the United States, particularly in light of recent controversy surrounding the widespread adoption of prenatal screening and low Down syndrome birth rates in Iceland. Critics argue that the Icelandic approach to prenatal testing has led to the abortion of nearly all pregnancies identified with Down syndrome, based on discriminatory attitudes toward persons with Down syndrome (Quinones and Lajka 2017). The Icelandic government maintains that the controversy is misleading, and that although it is the "responsibility of health-care personnel

to explain clearly and objectively what options a woman has," the choice of whether to conduct prenatal testing or abort a pregnancy is fully left to the mother (Ministry of Health 2017).

Medical Necessity

One of the major substantive requirements placed on the application of PGT is the limitation of its use to only situations of medical necessity, prohibiting the use of PGT for personal or social reasons. This may take the form of a requirement that the fetus be at "substantial risk" of "severe genetic disease" (Knoppers and Isasi 2004) or the criteria might remain undefined. Additional substantive requirements identified in our selected countries included prioritization of the welfare of the (future) child and treatability of the condition. Specifically, countries including a treatability requirement mandate that there be no treatment available at the time of diagnosis. Countries utilizing each of these criteria are outlined in Table 3. The most common criteria among the countries examined is a requirement that the condition being tested for is "serious" or "severe," as reflected in some form by regulations or guidelines in Australia, Austria, Canada, France, Germany, Japan, Netherlands, Singapore, and Switzerland.

Because most countries do not define which specific conditions meet the severity criteria, some room is left for debate. However, several countries have outlined more detailed criteria or specific conditions, demonstrating a range of restrictiveness. For example, Austria defines the severity of a condition by its outcome, allowing for PGT only in conditions in which

> the child becomes so ill during pregnancy or after birth that it 1. can only be kept alive by the constant use of modern medical technology or the constant use of other medical or nursing aids which severely impair his or her life, or 2. has severe brain damage or 3. in the long run will suffer from not effectively treatable severe pain and moreover, the cause of this disease cannot be treated. (Republic of Austria 1992 rev. 2018)

The United Kingdom and South Korea were the only countries in our sample that identify specific medical diagnoses for which PGT may be used. In South Korea, the 2005 *Bioethics and Safety Act* states that PGT may be used "only for diagnosing muscular dystrophy or any other hereditary disease specified by presidential decree" (Republic of Korea 2005). To date, 153 additional conditions have been approved by subsequent presidential decrees (Kim 2015). In the United Kingdom, conditions must be approved by the HFEA, the statutory body tasked with overseeing fertility treatment and research in the United Kingdom. At the time of this writing, more than 400 conditions had been approved, with at least 20 new conditions awaiting approval (HFEA n.d.).

There is no significant change apparent in the application of these criteria over time, with the exception of countries that previously prohibited the use of PGT. All countries in which we have identified a shift in the permissibility of PGT from prohibited to permitted now utilize the "serious or severe" criteria, along with other restrictive criteria, in line with continued restrictive attitudes toward PGT. The approach taken in South Korea and the United Kingdom of approving conditions on a case-by-case basis

Table 3. Criteria for allowing PGT

Criteria	Countries/States
Welfare of the child/embryo	Southern Australia (AU), Victoria (AU), Italy, Switzerland
Genetic defect (no severity criteria)	Victoria (AU), Brazil,[a] United States[a]
Significant risk	Western Australia (AU), Singapore,[a] Switzerland, United Kingdom
"Serious" or "severe"	Australia,[a] Southern Australia (AU), Western Australia (AU), Austria, Quebec (CA),[a] France, Germany, Japan,[a] Netherlands, Singapore,[a] Switzerland
Treatability	Austria, France, Germany, Netherlands, Switzerland
Specific conditions	South Korea, United Kingdom

[a]Suggested by guidelines.

requires a dynamic regulatory approach, increasing the scope of use each time a new condition is approved; however, the process itself does not appear to have changed significantly since being implemented. In countries with less specific criteria, however, shifts in interpretation of the severity required may not be reflected in the regulations themselves, as the interpretation of severity falls instead to the physicians and institutions providing PGT and within the private confines of the patient–doctor relationship.

In addition to severity, several countries discuss age of onset as a condition for approval; however, the age specified varies widely. Testing for conditions with onset beyond early childhood (particularly in the case of risk factors for adult-onset conditions with incomplete penetrance) faces criticism because of the excessive time, financial, and emotional cost for limited immediate benefit or effect on pregnancy outcome and raises questions regarding a (future) child's "right to an open future" (Kopelman 2007; Noble et al. 2008). In establishing a threshold for age of onset, countries must weigh these concerns against the individual reproductive liberties of the prospective parent(s), and the desire to prevent severe suffering even later in life. For instance, Germany prohibits testing for conditions with onset after age 18, whereas Switzerland permits testing for conditions with onset up to age 50. In the United States, guidelines from the ASRM suggest that testing for serious, untreatable adult-onset conditions is justified, and that testing for less penetrant or serious conditions may still be allowable.

Regulations in Australia, Belgium, and the United Kingdom include preimplantation HLA matching as an allowable condition for PGT. Although not specified by statute, the technique is also allowed or practiced in a number of other countries, including the United States, France, Brazil, Singapore, and Canada (Speechley and Nisker 2010; Bayefsky 2016). HLA matching is used in order to select for a child that will be able to serve as a hematopoietic stem cell donor for an existing sibling, often referred to as a "savior child" (Kakourou et al. 2017). The concept of savior siblings has stirred ethical debate, as the interests of the donor child, including potential risks of harm from PGT, the donation process, or emotional burden on the family, must be weighed against the medical benefit to the existing sibling. Although the success rate of HLA matching through PGT is limited, the procedure has gained increasing acceptance and more widespread use in recent years (Kakourou et al. 2018).

Nonmedical Sex Selection

One of the most heavily regulated and contentious applications of PGT is sex selection for nonmedical purposes. In nonmedical sex selection, preimplantation screening techniques can be used purposely to select embryos of a specific sex for personal or social reasons, rather than to avoid the selection of an embryo that may carry a sex-linked disease (Milliez 2007). However, the sex of an embryo may also be incidentally identified in the process of diagnosing another, medically indicated condition, at which point the provider (or the prospective parent[s]) must choose whether to utilize this information when selecting embryos to transfer (ASRM 2018).

The controversy over nonmedical sex selection weighs the potential for sex discrimination, particularly in light of historical sex discrimination practices in many countries, against the reproductive liberty of the individual (Milliez 2007). The vast majority of countries included in our sample weigh the former more heavily, adopting some sort of prohibition against or condemnation of nonmedical sex selection, as outlined in Table 2. In countries such as India, broad regulations place a blanket prohibition on prenatal sex determination by any means. In others, a prohibition on sex selection is included in legislation specifically focused on PGT. In spite of these prohibitions, sex selection by various methods appears to be widely practiced in several countries, including China and India, reflecting the limitations of even "hard" regulations that are not well supported by "soft" policies or social support (George 2006; Milliez 2007).

Three countries included in our sample allow some degree of nonmedical sex selection.

Israel, for instance, allows sex selection for "extremely exceptional, rare, and special cases," including for reasons of family balancing or harm to the "mental well-being" of parents or child (State of Israel Ministry of Health n.d.). The United States and Mexico are deemed to be the most permissive, having no legislation and few guidelines addressing sex selection. In each of these countries, sex selection is actively and increasingly practiced (Baruch et al. 2008; Whittaker 2011; Capelouto et al. 2018). However, professional organizations in the United States differ in their stances on this issue. The American College of Obstetricians (ACOG) has opposed the practice, whereas ASRM acknowledges the controversy surrounding nonmedical sex selection, yet stops short of prohibiting or encouraging the practice (ACOG 2007; ASRM 2015).

Conflicting Regulation, Reproductive Tourism, and International Norms

Because of the differences in regulation of PGT and other reproductive technologies across countries, cross-border travel for the purposes of seeking access to ART (or "reproductive tourism") is a significant topic of controversy and socioethical and legal concern (Spar 2005; Whittaker 2011). Through reproductive tourism, patients from countries with more restrictive regulations travel to countries with more permissive (often private ordering) ones to receive fertility treatments, including PGT, which they would not otherwise be eligible for in their home country. In this manner, they seek to avoid restrictions on access to such reproductive services in general, but also to controversial ones (e.g., nonmedical sex selection), or to obtain lower-cost services. The United States and Mexico, the most permissive countries in our sample, are commonly cited as destinations for reproductive tourism (Blyth 2010). Reproductive tourism pits individual reproductive autonomy and open international commerce against the attempts of each country to regulate the use of PGT by their own citizens in a way that reflects prevailing societal values.

Reproductive tourism made headlines around the world with the birth of the first child born following mitochondrial replacement therapy (MRT), which occurred in Mexico in 2016 (Zhang et al. 2017). In this case, MRT was performed by a U.S.-based researcher for Jordanian parents, sparking global controversy (Chan et al. 2017). Although there are significant differences in the technologies and ethical concerns involved in MRT and PGT, this case shone a spotlight on the way permissive scientific and medical regulations can encourage cross-border travel for access to reproductive services.

Some attempts have been made to harmonize or bring these differing regulations in line with each other, particularly in Europe. As previously described, the European Court of Human Rights has ruled that access to PGT (at least in cases of medical necessity) is protected under the Convention for the Protection of Human Rights and Fundamental Freedoms, to which the 47 member states of the Council of Europe are held (Council of Europe n.d.; ECHR 2012). The Council of Europe Convention on Human Rights and Biomedicine (referred to as the Oviedo Convention) outlines more restrictions, limiting all predictive genetic testing to use "only for health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counseling" and prohibiting nonmedical sex selection (Council of Europe 1997). As of 2017, the Oviedo Convention had been ratified by 29 European countries, including those from our sample.

CONCLUDING REMARKS

PGT is subject to a wide array of regulatory approaches, which vary significantly by country. Although international regulations exist, they apply only to countries that choose to ratify and enforce them. Similarly, the strength of self-regulatory policy is predicated on voluntary compliance. In the course of our analysis, we observed a recent trend toward more permissive regulation of PGT, in both private and publicly ordered countries as well as at both ends of the permissibility spectrum. This shift may be driven by advances in technology, changes in cul-

tural attitudes, or court-driven alterations to legal practice. Medical necessity remains, to varying degrees, a common criterion for eligibility in more restrictive countries, a term that goes generally ill-defined and therefore necessarily subject to local interpretation. PGT for nonmedical purposes is actively practiced in countries with permissive regulation, yet does not necessarily follow a market or an unfettered laissez faire model. Although genetic counseling is widely accepted and encouraged by professional guidelines, only a few countries require it by legislative mandate. Because genetic counseling does not exist as a profession in all of these countries, the responsibility for providing counseling often falls to the physicians providing PGT. These conflicting regulatory approaches are certainly a driver of cross-border travel for reproductive purposes.

During the last decade, the regulation of PGT has followed mostly a linear path, with incremental changes driven by scientific advances as well as greater societal uptake. No longer considered an experimental practice, stakeholders across the world have challenged the status quo, recognizing that both technological and policy developments do not take place in a moral vacuum. They have done so under the flag of reproductive freedom, equitable access, and welfare considerations, among other ethical concerns. Despite the passage of time, the ubiquitous presence of eugenic fears constantly casts a shadow over technologies that open the door for selecting the genetic characteristics of a human offspring. For this reason, we predict that despite greater societal acceptance, widening the permissibility criteria for PGT will remain controversial and a matter of continued social and policy debate. Our hope is that such debates and ensuing changes in the regulatory landscape will always be inclusive so as to consider the voices of those who will ultimately be affected.

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