

Chapter 2

Elements of Informed Consent for Preimplantation Genetic Diagnosis

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Introduction

The concept of informed consent exists to protect patients and research subjects from undue harm. To achieve valid informed consent, individuals should be informed of the relevant risks, comprehend the information provided, and voluntarily agree to take part in either a research study or a medical treatment [1–3]. Since PGD typically involves the biopsy of one or more cells from an in vitro fertilized early embryo followed by genetic analysis of the biopsied cells, achieving valid informed consent is especially challenging. First, the informed consent for PGD must include information about the risks associated with the three key components of the process: in vitro fertilization (IVF) using intracytoplasmic sperm injection (ICSI) to generate embryos, the embryo biopsy, and the genetic testing [4]. Furthermore, prospective parents should be aware not only of risks to themselves, but they must also be aware of risks to the resulting child and understand that they are consenting on behalf of the future child. As such, potential risks to the resulting child must be carefully outlined in the information provided to prospective parents [4, 5].

Given the complicated and multifaceted nature of PGD, it is essential that prospective parents be provided the relevant information in a manner conducive to comprehension of the associated risks. To this end, prospective parents should be provided with information in different formats and through different mechanisms and be given ample opportunities to have their questions answered [3]. There will ideally be different stages of informed consent, beginning with accurate and up-to-date educational material about risks on fertility center websites [5, 6]. Conversations about risks associated with PGD should also take place with fertility center staff and genetic counselors. It may also be wise to go over more difficult to comprehend

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aspects of the material multiple times throughout the consent process [7]. Some have suggested the use of audiovisual aids in addition to individual counseling and written documentation as mechanisms by which to inform patients prior to obtaining consent [7, 8]. Furthermore, full consent to PGD should be obtained before the in vitro fertilization (IVF) process begins, so that there are no time and financial pressures when prospective parents are making decisions.

In addition to being informed, consent must also be voluntary [3]. Fertility centers should take special care to ensure that prospective parents are not being inadvertently pressured into choosing the procedure. As such, any financial conflicts of interest or other such conflicts that might lead to undue pressure from the fertility center should be shared with prospective parents [9, 10]. It is also important that prospective parents are provided with unbiased information regarding risks so that they can carefully consider whether to initiate a PGD cycle. While there are many important elements of valid informed consent for PGD, this review will detail the risks associated specifically with the embryo biopsy and genetic testing components of PGD and provide suggestions regarding content that should be discussed with prospective parents. However, it is essential that prospective PGD users also be informed of the risks associated with IVF and ICSI, as these more widespread procedures are done before the embryo biopsy and testing components of PGD.

Categories of Consent Specific to PGD

Risks Associated with Embryo Biopsy

While informed consent procedures for PGD often cover risks to the mother, the risks to the fetus and future child are less often reported [4–6]. Some fertility center websites make reference only to studies that have found no increased risks associated with PGD. However, there are published, peer-reviewed studies that have detected subtle neurological and other differences in offspring born following embryo biopsy. While these studies are by no means definitive, they certainly warrant disclosure in the proper context to prospective parents as part of the informed consent process. This section examines the existing scientific studies of the risks to resulting fetuses and children from embryo biopsy procedures and also outlines studies indicating that preimplantation genetic screening (PGS) may decrease the chance of live birth.

Types of PGD Safety Studies

A number of mouse and human studies have addressed the issue of embryo biopsy safety in PGD/PGS, resulting in a complicated set of findings. The first complicating factor in interpreting the data is that studies have been performed in both mice and humans. Mouse studies can be quite advantageous in that they allow for large

sample sizes, more invasive and thorough analysis of offspring, and carefully controlled study design, yet embryo development in the mouse is not the same as in humans. Therefore, any interpretation of mouse studies must be made with this in mind. Even two different mouse strains can give strikingly different results [11]. Therefore, it is hard to know if findings in mice will translate to humans. However, that doesn't mean that only findings from human studies should be considered when evaluating the safety of PGD.

The second complicating factor in assessing safety studies is that study design varies markedly in published reports. A number of studies lack matched controls and very few studies report blinded analysis of outcomes. Furthermore, an important limitation of the published retrospective studies is the possibility of selection bias, as could happen if parents of children with health problems are more or less likely to enroll in a trial. Selection bias can also occur if fetuses that have been biopsied as embryos are more likely to be tested prenatally and aborted as a result of an abnormal finding.

A third complication when interpreting safety studies is that the type of biopsy used also varies when comparing studies. The three main types of preconception and embryo biopsies include polar body biopsy, day 3 cleavage-stage embryo biopsy of one or two blastomeres, and day 5 blastocyst biopsy of multiple trophectoderm cells [12, 13]. Therefore, patients should be informed not only about the results of the published safety studies but also about any important differences in embryo biopsy methodologies used by individual centers compared to those described in the published literature. A fourth complication with the existing safety studies is the limitation of time. No long-term human safety study has followed PGD offspring through adulthood, nor has any study examined the effects of PGD on the offspring of biopsied individuals. Given the potential challenges associated with assessing the safety of the embryo biopsy procedure, it is important that prospective parents are provided a balanced view of all published safety studies and made aware that no long-term safety studies have yet been completed in humans.

Results of PGD Safety Studies in Mice

While many studies have detected no increase in congenital or other abnormalities in PGD offspring [14], there is a trend in the detection of neurological abnormalities in embryo-biopsied offspring across different studies and in both mice and humans. In this section, the mixed results reported in published studies with mice are summarized.

There have been a number of studies examining the effect of embryo biopsy on fetal development, but the interpretation of these results is complicated by the different mouse strains and different developmental stages at which the biopsies occurred. For instance, a study in which one blastomere was removed at the four-cell mouse embryo stage found significant decreases in preimplantation development to the blastocyst stage and in live fetus development [11]. However, these differences were unique to the C57/BL6 strain in that no statistically significant

developmental abnormalities were seen in the B6D2F1 strain. In a different study in which one blastomere was biopsied at the eight-cell stage, hatching was premature and sometimes abnormal in biopsied mouse embryos compared to controls, yet no differences in global gene expression were found 28 h post-biopsy [15]. In a more recent study, mouse fetuses that had one cell removed at the four-cell embryo stage had significantly lower weight, lower levels of some steroid clearance enzymes in the placenta and fetal liver, and differences in steroid hormone levels in the placenta, fetal blood, and fetal liver when compared to controls [16]. Taken together, these data suggest that some but not all aspects of embryo and fetal development may be altered as a result of embryo biopsy in the mouse.

Several studies have also looked at later stages of mouse development following embryo biopsy. In one study, analysis of adult mice which underwent biopsy of a single blastomere at the eight-cell embryo stage revealed no abnormalities in blood cell counts, blood chemistry, and organ histology compared to controls [17, 18]. However, in another study, Yu and colleagues demonstrated that murine embryos which underwent biopsy at the four-cell stage performed less well than non-biopsied mice on a memory test [19]. This same study demonstrated that biopsied mice had altered expression of proteins implicated in neurodegenerative disease, suggesting the potential for long-term neurological abnormalities in biopsied mice. Furthermore, biopsied mice had altered levels of stress hormones both before and after cold stress challenge, and biopsied mice had more lipid storage in the adrenal cortex compared to controls [20]. Thus, while a number of measured outcomes have been normal in biopsied mice, the embryo biopsy procedure is associated with a variety of health problems in mice. The informed consent process for PGD should include reference to the findings from mouse studies, while at the same time making it clear that mouse outcomes may or may not translate to humans.

Results of PGD Safety Studies in Humans

Results of PGD safety studies in humans have been more promising when compared to some of the mouse studies. In an observation of the first 109 children born following polar body biopsy at the Reproductive Genetics Institute, no significant abnormalities were detected in birth weight of offspring and no increase in congenital abnormalities over the published literature for naturally conceived births was reported [21]. In another observational report of outcomes following one- or two-cell biopsy of day 3 embryos at the Centre for Medical Genetics, no significant increase in congenital abnormalities was reported [22]. However, there was a significant increase in the number of perinatal deaths and stillbirths following embryo biopsy [22]. A different observational study found that PGD offspring had low birth weight as well as decreased motor and cognitive abilities [23]. Of note, all of these studies lacked a matched control group of either ICSI and/or naturally conceived children [21–23]. While observational studies can provide important clues to issues such as the safety of embryo biopsy, it is difficult to draw clear conclusions in the absence of a matched control group.

A number of controlled studies have been carried out, however, and some of those results have been reassuring. In a controlled study comparing ICSI and naturally conceived (NC) children to PGD/PGS children who underwent one- or two-cell blastomere biopsy at the eight-cell stage, there were no statistically significant differences in mental and psychomotor development of singletons at age 2 [24]. Furthermore, no statistically significant differences were seen in language or socio-emotional development when comparing PGD/PGS, ICSI, and NC 2-year-olds [25]. A follow-up analysis of twins also revealed no statistically significant differences in mental, motor, socio-emotional, and language development in PGD/PGS offspring compared to ICSI or NC children at age 2 [26]. In addition, Desmyttere and colleagues reported no statistically significant difference in major or minor malformations in PGD/PGS offspring [27, 28]. However, BMI and arm circumference were lower in PGD/PGS offspring compared to ICSI and NC children [28]. In a matched control trial with blinded analysis, PGD offspring had significantly lower gestational age at birth and a higher number of births with low birth weight. In this same study, PGD offspring scored lower on the Locomotor subscale, yet higher on the Hearing and Language subscales of the Griffiths Scale [29]. Thus, outcomes based on these controlled trials demonstrated many similarities between biopsied offspring and controls, but a number of statistically significant differences were also observed. It is also important to keep in mind that selection bias, as might occur if fetuses with abnormalities are more often detected and aborted following embryo biopsy, can be an important limitation of such trials.

Addressing the issue of selection bias, Middelburg and colleagues reported on the results of a randomized, controlled, blinded, prospective study in which PGS offspring were compared to IVF offspring [30]. Individuals in the PGS group typically had one blastomere removed at the four-cell embryo stage, although two blastomeres were taken when necessary for analysis. Consistent with other studies, no increase in minor or major abnormalities was seen in the PGS group at birth [31]. While there were no statistically significant differences in outcomes at 18 months of age, PGS children did have an increased incidence of mild fine motor dysfunction and mildly dysfunctional posture/muscle tone. Furthermore, PGS children had more severe issues at the individual level as compared to controls [30]. At age 2, PGS and IVF offspring had similar mental, psychomotor, and behavioral scores. However, the neurologic optimality scores were statistically significantly lower in the PGS group [32]. At age 4, no differences in blood pressure or anthropometrics or received medical care were observed, yet a statistically significant increase in paramedical care (speech, physical, or occupational therapy) was seen in the PGS group [33]. Also at age 4, there were no neurological, cognitive, or behavioral differences between singleton groups. In contrast, embryo biopsy in twins was associated with “a negative effect on neuromotor condition and a positive one on sequential processing” [34]. Since some neurological deficiencies only become apparent later in life, it will be important to follow embryo-biopsied children into school age years and beyond to more carefully assess any potential adverse neurological and other outcomes [30]. These potential safety risks should be carefully weighed against the potential benefits before making a decision to move forward with the procedure [35].

Chance of Live Birth

A number of studies have examined the chance of live birth following PGD/PGS. Based on the most recent ESHRE PGD Consortium data published, the delivery rate following embryo transfer was 25 % for PGD done following testing for structural chromosomal abnormalities, 30 % for sex determination for X-linked diseases, and 25 % for evaluation of embryos for monogenic diseases [14]. These PGD data are in contrast to a 22.8 % delivery rate per embryo transfer seen following PGS [14]. However, data looking at IVF alone were not part of this collection. A meta-analysis of randomized control trials demonstrated a reduction in the chance of live birth from 26 % with IVF alone to 13–23 % with IVF and PGS [36]. Taken together, these data suggest that the chance of live birth may be reduced following PGS as compared to IVF alone or PGD. However, these data may be misleading as the indication for PGS is different than for PGD, with PGS being indicated for prospective parents who have a higher risk of pregnancy loss. In a different retrospective cohort study evaluating PGD outcomes in Sweden, it was found that the chance of pregnancy is doubled with one-cell biopsy as compared to two-cell biopsy of cleavage-stage embryos [37]. Thus, prospective parents should be informed that the chance of live birth might be reduced following PGS and that two-cell biopsies may reduce the chance of live birth as compared to one-cell biopsies.

Important Components of Embryo Biopsy Informed Consent

- Studies examining the risks of embryo biopsy to the fetus and future child have been performed in mice and humans. Some have found no risk from the procedure, while some have found neurological and other abnormalities and a higher incidence of children requiring developmental support following embryo biopsy.
- Results from mouse studies do not always translate to humans, but mouse studies can allow for more controlled study design and detailed analysis of offspring. Mouse studies should not be overlooked.
- No long-term study has been done in human children past the age of 4. Risks to older children, adults, and their offspring are unknown.
- There is some evidence that embryo biopsy may reduce the live birth rate.

Risks Associated with Genetic Testing of Biopsied Cells

Given the imperfect nature of genetic testing of embryos, there is a chance of misdiagnosis even when the testing is done by an experienced center. Prospective parents should be made aware of the need for prenatal testing if they wish to confirm the embryo testing results. Furthermore, comprehensive genetic testing, in which a wide range of genetic information will be determined, may reveal unanticipated

genetic information about the tested embryos that parents or the resulting child may not wish to know. Furthermore, selection of embryos with a decreased risk of a known disease may also inadvertently select for embryos with an increased risk of an unknown disease. Finally, genetic testing to determine the suitability of an embryo for implantation has larger societal implications.

Possibility of Misdiagnosis

Misdiagnosis can occur for a variety of reasons, and it is important that potential PGD patients be informed of this possibility. Causes of misdiagnosis include human error, PCR or FISH errors, mosaicism, unprotected sex, uniparental disomy, and many others [38]. Human error in the lab, such as tube mislabeling, is one other cause of misdiagnosis that can be reduced substantially if proper quality control measures are in place [38]. While not technically a misdiagnosis, unprotected sex can lead to natural fertilization and the subsequent development of an unselected embryo even if a selected embryo is transferred. Couples should be made aware of the risks associated with unprotected sex before beginning IVF/PGD. Another factor that can lead to transfer of an unselected embryo is mosaicism. While FISH or PCR-based analysis of the biopsied cell may in fact be accurate, mosaicism can lead to the transfer of an unselected embryo if the biopsied cell is not representative of the other cells remaining in the transferred embryo [38].

PCR-based diagnosis of biopsied cells can also result in misdiagnosis for reasons other than mosaicism. Often cited reasons for PCR-based misdiagnosis are contamination and allele dropout [38]. In an embryo reanalysis study, Dreesen and colleagues found that the initial analysis of 881/940 embryos was consistent upon reanalysis [39]. Most cases of misdiagnosis were due to mosaicism, with allele dropout and contamination cited as other reasons for misdiagnosis in their study. When the researchers further analyzed the data, they found that PCR analysis of a two-cell embryo biopsy is more accurate than analysis of a one-cell biopsy. Specifically, 3.3 % of two-cell embryo biopsies were misdiagnosed and 8.4 % of one-cell embryo biopsies were misdiagnosed by PCR [39]. Other reports of misdiagnosis, typically identified prenatally or after birth, cite lower rates of PCR-based misdiagnosis [14, 38]. Misdiagnosis rates for FISH have been cited as 0.06 and 0.07 % [14, 38], and FISH-based diagnosis has historically been considered more accurate than PCR-based diagnosis. However, a recent study found the misdiagnosis rate to be higher in FISH than in PCR [14].

Since there are risks of error associated with PGD, even when it is done properly, some lawsuits have been aimed at the lack of adequate informed consent regarding full disclosure of the risks of error that can lead to PGD misdiagnosis [40]. Surprisingly, only a minority of ESHRE Consortium members had a formal quality control program in place in 2008 to check the accuracy of PCR-based diagnosis of biopsied embryos [39]. Therefore, it is important for centers to give their own misdiagnosis rates if they have accurate ones and provide published rates as well. Given

the chance of misdiagnosis, a Practice Committee report recommends informing patients that prenatal testing can be done using amniocentesis or CVS to confirm PGD results [41]. The risks associated with these prenatal testing procedures should also be provided to prospective patients before initiating IVF/PGD.

Comprehensive Genetic Testing

Genetic testing of biopsied cells initially targeted just a single or several defined genes. However, advances in technology have made comprehensive genetic testing of biopsied cells possible. Since comprehensive genetic testing will likely reveal variants of unknown significance, information about the risk of late-onset disease, as well as nonmedical characteristics, it is important that prospective parents are aware of the risks associated with learning this type of information about their future children. A variety of suggestions have been put forth regarding how much information prospective parents should be given during the informed consent for genetic testing [42]. Ideally, informed consent would only occur after full disclosure and understanding of the details of the genetic testing. However, given the complex nature of comprehensive genetic testing, it may not be feasible to provide prospective parents with all details regarding what the test results might reveal because of concerns that comprehension may be compromised if the information provided is too complicated [42, 43].

To address the concern that consent may be inadequate if there is too much information given during the consent process, some have advocated for a generic form of informed consent for genetic information [8]. In fact, six categories of information have been proposed, including “congenital lethal disorders; early- or late-onset disorders requiring intensive medical care; early- or late-onset disorders requiring limited medical care; susceptibilities for complex disorders; conditions involving only minor health problems; and abnormal findings of which the clinical implications are unknown” [44]. However, this type of grouping can be problematic because of the different ways that doctors and parents might classify specific genetic risk information [44, 45]. Even the label of “abnormal” when applied to findings of unknown significance is potentially misleading, as many apparently healthy individuals have copy number variants and other DNA changes [46]. Furthermore, a recent study demonstrated that greater than 40 % of healthy individuals have mutations in genes that are predictive of severe early-onset disease [47]. Thus, it is not possible to predict with complete accuracy the health consequences of many genetic alterations that may be found as a result of comprehensive genetic testing [48]. Given the uncertainty regarding the predictive nature of many genetic test results, it is essential that prospective parents are aware of these limitations.

To address the limitations associated with providing only generic or specific information, Bunnik and colleagues instead offer a hybrid model in which generic consent (including categories of information as has been suggested by others) is the foundation, and then a well-organized list of specifically tested diseases is included

as well [49]. This concept is in line with the suggestion by Elias and Annas that specific consent should still be obtained for certain tests such as the genetic test for Huntington's disease [8]. Furthermore, Bunnik and colleagues suggest that consumers be required to actively select for/against different types of tests because such active decision making will aid the informed part of the consent process. While not formally part of the consent, some have also suggested that prospective parents be given the option to receive more detailed information about any of the genetic categories [49, 50]. Since specific genetic risk information will likely change over time, it will be important to constantly update this component of the consent process as new risks arise.

In addition to being informed about what the test will reveal, parents should also be involved in determining what information will be shared with them after the results have been determined [42]. In discussing prenatal genetic testing, de Jong and colleagues argue that information about late-onset disease should only be given to a woman if she plans to abort such a fetus (or in the case of PGD, not transfer an affected embryo). This thinking is in line with ethical concerns many have regarding the genetic testing of minors for late-onset disease [51]. However, because some prospective parents may not follow through with plans to avoid transfer of embryos with increased risk of late-onset disease (if testing reveals that all biopsied embryos have an increased risk of at least one late-onset disease), children could still be born with such knowledge [44]. Even if the parents don't share this information with their children, just having this knowledge may hinder the child's right to an open future [42]. Thus, it is important that prospective parents are aware of the type of information that genetic testing can uncover and that parents carefully consider what the future child might want to know about himself or herself when determining the type of genetic information that should be revealed. A delicate balance will need to be struck between a child's right to an open future and the reproductive freedoms of prospective parents, and the solution may involve limiting the type of information that is shared with parents regarding embryos that will ultimately be implanted.

Inadvertent Selection for Increased Disease Risk

It is important that prospective parents understand that by selecting against an embryo with a particular disease risk or other characteristic, they may at the same time be inadvertently selecting for an embryo with an increased risk of a different disease. This inadvertent selection could happen in the case of linked genes or as a result of heterozygote advantage [52]. For example, the disease sickle cell anemia occurs when an individual has two mutant copies of the β -globin gene [53]. However, heterozygous individuals with only one abnormal copy of the β -globin gene are less susceptible to malaria caused by the parasite *P. falciparum* [54, 55]. Therefore, while selection of embryos free of the β -globin gene mutation will virtually

eliminate the risk of sickle cell anemia in the offspring, these same offspring will also be more susceptible to malaria.

While less well characterized than the sickle cell example, many have argued that the high incidence of mutant cystic fibrosis transmembrane conductance regulator (CFTR) genes is also a result of heterozygote advantage [52]. The CFTR gene codes for a chloride channel, and individuals with two mutant CFTR genes often have cystic fibrosis. It is possible that having one mutant CFTR gene confers some protection against either diarrheal diseases or typhoid fever [52]. Given the complexity of the human genome, inadvertent selection of embryos with increased disease risk should be taken seriously, especially when prospective parents choose to select for nonmedical traits. In trying to avoid specific diseases or characteristics in their offspring, some prospective parents might be unknowingly selecting embryos that will result in future children with increased risk of unknown diseases.

Social Implications of PGD

The use of PGD and other technologies to select the characteristics of offspring has important societal implications that should be made clear to prospective parents [56]. While there is an inclination by some to assume that any deviation from “normal” is something to be avoided, many in the disability community have argued that those with disabilities can lead rich and meaningful lives and there are potential harms associated with seeking “perfection” [57]. Along those lines, in 2008 the United States passed the Prenatally and Postnatally Diagnosed Conditions Awareness Act, requiring that parents be given accurate and balanced information regarding the life experiences of someone with a particular disease so that they can make a more informed decision regarding whether to terminate a particular pregnancy or give a child up for adoption [58]. This type of awareness should be applied to the consent for embryo testing as well.

In addition to potential harms associated with selecting against future children who may deviate from what is considered “normal”, nonmedical trait selection can also lead to harms at a societal level. In part due to reproductive freedoms, sex selection is permitted in the United States. However, this type of selection can lead to population-level imbalances in the sex ratio. As has been seen in countries practicing sex-based infanticide and selective abortion, the resulting skewed sex ratios have led to a host of downstream problems including female trafficking [59]. Furthermore, differences in access to PGD are likely to lead to further inequalities between people of different socioeconomic or racial groups [60]. Especially in regions where the more controversial uses of PGD are not regulated, prospective parents should be aware of these larger societal issues so that they can make their own informed choices.

Important Components of Genetic Testing Informed Consent

- There is a potential for error in the genetic testing of biopsied cells, which could lead to implantation of an embryo with the characteristic parents were trying to select against.
- Since there is this chance of misdiagnosis when biopsied cells are tested using FISH or PCR, prenatal testing may be required to confirm embryo test results. As such, the risks associated with prenatal testing should be disclosed during the consent for PGD.
- If comprehensive genetic testing is done on biopsied cells, unanticipated information regarding long-term health risks to the future child may become known. A child's right to an open future should be carefully considered when determining the type of genetic information that will be shared with parents regarding implanted embryos.
- Selection for embryos with certain genetic compositions may also inadvertently select for embryos with an increased risk of other diseases.
- There are important social implications associated with selection of future offspring based on genetic information.

Conclusion

In addition to being informed about potential risks associated with PGD, prospective parents should also be made aware of alternatives to the procedure. For instance, if prospective parents wish to select certain characteristics, they may choose to use donor gametes, adopt, or selectively terminate a pregnancy. It is especially important that prospective parents understand that in using PGD to select embryos with certain characteristics, they may in fact be harming those “preferred” embryos during the biopsy and selection process. Finally, it may be possible in the future to carry out less-invasive embryo selection using methods such as the testing of DNA in the blastocoele fluid [61–63]. Prospective parents will need to balance their wishes to have a child with certain characteristics with the possibility of directly or indirectly harming that child through the PGD procedure.

Note Added in Proof While this chapter was in production, Winter and colleagues reported no significant differences in measured cognitive and psychomotor outcomes in 5 and 6 year old Caucasian PGD singletons. In addition, Sacks and colleagues reported on neuropsychological findings of a pilot study of 4 and 5 year old PGD children [64, 65].

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