Cancer Genetic Testing and Assisted Reproduction

Kenneth Offit, Kelly Kohut, Bartholt Clagett, Eve A. Wadsworth, Kelly J. Lafaro, Shelly Cummings, Melody White, Michal Sagi, Donna Bernstein, and Jessica G. Davis

ABSTRACT

Purpose
Because of increasing uptake of cancer genetic testing and the improving survival of young patients with cancer, health care practitioners including oncologists will increasingly be asked about options for assisted reproduction by members of families affected by hereditary cancer syndromes. Among these reproductive options, preimplantation genetic diagnosis (PGD) offers the opportunity to select embryos without familial cancer-predisposing mutations.

Methods
A review of the published literature supplemented by a survey of PGD centers in the United States.

Results
Prenatal diagnosis and/or embryo selection after genetic testing has already been performed in the context of more than a dozen familial cancer syndromes, including the common syndromes of genetic predisposition to colon and breast cancer.

Conclusion
While constituting new reproductive options for families affected by cancer, the medical indications and ethical acceptance of assisted reproductive technologies for adult-onset cancer predisposition syndromes remain to be defined. Continued discussion of the role of PGD in the reproductive setting is needed to inform the responsible use of these technologies to decrease the burden of heritable cancers.

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INTRODUCTION

During the next decade, health care professionals, including oncologists will be increasingly involved in discussions of reproductive options when providing genetic testing to patients and their families affected by hereditary cancer syndromes. This trend will be driven by several factors, including the expanding clinical availability of genetic tests that predict risk of pediatric and adult cancers, the improving survival and prospects for childbearing after cancer treatment, and increasing access to new technologies that utilize genetic testing to guide reproductive choices. Already a substantial literature exists regarding the use of cancer genetic testing for prenatal diagnosis or to guide embryo selection before implantation (preimplantation genetic diagnosis [PGD]). These remarkable innovations in reproductive medicine also raise important ethical, social, and legal issues that must be addressed to ensure the most responsible translation of these new technologies to clinical practice.

STATE OF REPRODUCTIVE TECHNOLOGIES

Following the identification of a disease-associated mutation in a family, reproductive technologies currently available include conventional prenatal (postimplantation) assessment utilizing chorionic villi or amniotic fluid cell sampling and genetic analysis, as well as newer methods to perform genetic analysis before implantation of an early embryo. Chorionic villus sampling (CVS) may typically be offered to patients between weeks 10 to 12 of gestation, and amniocentesis is usually performed at 16 to 20 weeks. On the basis of the results of these tests...
and patient choice, there is an option whether or not to continue the pregnancy. PGD emerged in 1990 in conjunction with the increased use of in vitro fertilization (IVF) and further advances in chromosome identification techniques and molecular diagnostics. PGD allows for the selection of genetically tested embryos which may then be transferred back to the uterus. At present, a few dozen centers worldwide have the technical capability and expertise to perform the procedure for single-gene disorders. Major requirements for performance of PGD, in addition to assisted reproduction technology (ART), include the expertise to perform micromanipulation of embryos, and to conduct single-cell diagnostic genotyping or chromosome analysis. Additionally, although considered to be approximately 97% accurate depending on the condition being tested and testing methodology, PGD is still considered by many as a technology under development, requiring confirmation through prenatal diagnosis.

PGD utilizes embryos resulting from IVF, fertilization that occurs outside of the mother’s womb. Such embryos are at the earliest stage of development, before the time (6 days postconception) when implantation typically occurs. There are several techniques to sample DNA at this early stage without having an impact on the viability of the conceptus. These include biopsy of the first and second polar bodies (polar body removal) when a mutation is maternally inherited, aspiration of one or two cells from a six to eight cell embryo at 2 to 3 days postconception (blastomere biopsy; Fig 1), and, although rarely performed, biopsy of the trophoderm taken from an embryo at the blastocyst stage. Some authors prefer polar body biopsy because it does not result in a decrease in embryonic cell number and because of other technical considerations. Recently, the cryopreservation of biopsied embryos has proven a viable option when additional unaffected embryos exist and are not transferred during the cycle of origin.

A recent review of major PGD centers indicated that approximately 6,000 to 7,000 PGD cycles have been performed worldwide, resulting in more than 1,000 live-born infants. Although previously reported to be increased after IVF, no excess in congenital anomalies was noted after PGD, and a misdiagnosis rate, not including technical failures, of approximately 2% was reported by a European PGD consortium. Although long-term studies of outcomes after PGD have not been performed, recent reports have raised a concern over the possible association between assisted reproduction and imprinting defects caused by epigenetic dysregulation. PGD for cancer predisposition syndromes has been carried out at select referral sites, where both embryo biopsy and single-cell genotyping are performed, or at a number of specialized IVF centers where the single-cell biopsy is performed and sent to a reference laboratory for analysis. Depending on which of the models is chosen, the cumulative cost of PGD and IVF for single-gene disorders can be as high as $12,000 to $15,000 per cycle, most of which is not routinely covered by insurers. Some insurance plans may cover the IVF component of PGD, when infertility is present, but consider PGD “for the purposes of identifying embryos with possible predispositions to late-onset disorders [eg, cancer]” as “not medically necessary.”

### RESULTS

A review of the literature revealed 55 case reports of prenatal or preimplantation diagnosis performed in the setting of cancer predisposition syndromes. Thirteen PGD centers self-identified as providing clinical and/or research services on www.genetests.com (Appendix Table A1, online only). Each was contacted by phone or e-mail, and/or Web sites reviewed to assess availability or performance of PGD for cancer syndromes. Nine of the 13 centers indicated that they had either performed PGD for single-gene cancer predisposition syndromes or were in the process of providing such services. Results of the literature review and phone survey by syndrome are shown in Table 1.

#### Recessive Disorders

A relatively small number of genetic predispositions to cancer are inherited in an autosomal recessive manner. If both parents are mutation carriers, there will be a one in four chance of having a child affected by the condition and a three in four chance of having a healthy child. In such a setting, depending on the severity of the genetic condition, many parents may elect termination of pregnancy after prenatal testing. For example, the incidence of Tay Sachs disease, a non–cancer-related syndrome, has been reduced by more than 90% since carrier screening was introduced in the 1970s.

Among the recessive cancer predisposition syndromes, the characteristic phenotypes include chromosomal instability, defects in DNA damage response, and immunodeficiency. Chief among the chromosomal instability syndromes is Fanconi anemia (FA), a rare disease associated with an increased risk for leukemia. Prenatal diagnosis has been discussed as an option in the context of genetic counseling at the relatively limited number of academic centers specializing in this disorder. Following the identification of FANCD1 as BRCA2, it was observed that in rare kindreds, the presence of two BRCA2 mutations was associated with a median age of onset of 3.5 years for brain tumors and 2.2 years for leukemia. This suggests a role for prenatal diagnosis for pregnancies in which both parents are found to be BRCA2 mutation carriers. Because of the high carrier frequency (1%) for the 6174delT BRCA2 mutation among
Ashkenazi Jews, we recommended that all Ashkenazi reproductive-age partners of a spouse with a BRCA2 mutation be screened for this BRCA2 allele.\textsuperscript{18}

Other recessive cancer predisposition syndromes for which pre-natal genetic diagnosis has been performed include Bloom syndrome (BS),\textsuperscript{20,21} mosaic variegated aneuploidy (MVA),\textsuperscript{22} ataxia telangiectasia (AT),\textsuperscript{23} Nijmegen breakage syndrome (NBS),\textsuperscript{24,25} xeroderma pigmentosum,\textsuperscript{26} Wiskott-Aldrich Syndrome,\textsuperscript{27-29} X-linked lymphoproliferative disease (XLP),\textsuperscript{30,32} and some forms of human severe combined immunodeficiency.\textsuperscript{33-37}

Homozygosity of mutations in the MYH gene has recently been implicated in a polyposis syndrome with a markedly increased risk for

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### Table 1. Case Reports of PND or PGD for Cancer Susceptibility Syndromes.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Genes</th>
<th>Major Component Tumors</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recessive disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>FANCA, C, D1, D2, E, F, G, L, I, J</td>
<td>Leukemia, esophageal cancer, skin carcinoma, hepatoma</td>
<td>16,17</td>
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<tr>
<td>Bloom syndrome</td>
<td>BLM</td>
<td>Leukemia, carcinoma of the tongue, esophageal cancer, Wilms tumor, colon cancer</td>
<td>20,21</td>
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<tr>
<td>Mosaic variegated aneuploidy</td>
<td>BUB1B</td>
<td>Rhabdomyosarcoma, leukemia, nephroblastoma</td>
<td>22</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>ATM</td>
<td>Leukemia, lymphoma, ovarian cancer, gastric cancer brain tumors, colon cancer</td>
<td>23</td>
</tr>
<tr>
<td>Nijmegen breakage syndrome</td>
<td>NBS1</td>
<td>Lymphoma, glioma, medulloblastoma, rhabdomyosarcoma</td>
<td>24,25</td>
</tr>
<tr>
<td><strong>MYH-associated colon cancer predisposition</strong></td>
<td>MYH</td>
<td>Colorectal cancer</td>
<td>NCR</td>
</tr>
<tr>
<td>Xeroderma pigmentosum</td>
<td>XPA, B, D, G XP variant</td>
<td>Skin cancer, melanoma, leukemia</td>
<td>26</td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>WAS</td>
<td>Hematopoietic malignancies</td>
<td>NCR</td>
</tr>
<tr>
<td>X-linked lymphoproliferative disease</td>
<td>SAPSH2D1A</td>
<td>Lymphoma</td>
<td>22-29</td>
</tr>
<tr>
<td>Severe combined immunodeficiency</td>
<td>ADA, IL7Ra, RAG1, RAG2, Artemis, CD45, Jak3</td>
<td>B-cell lymphoma</td>
<td>NCR</td>
</tr>
<tr>
<td><strong>Dominant disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal cancer</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
<td>Colon cancer, endometrial cancer, ovarian cancer, renal pelvis tumors, stomach and small bowel cancers</td>
<td>NCR ††</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>TP53</td>
<td>Breast cancer, soft tissue sarcomas, leukemia, osteosarcoma, brain tumors, adenocarcinoma</td>
<td>41,42</td>
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<tr>
<td>Familial adenomatous polyposis</td>
<td>APC</td>
<td>Colon cancer</td>
<td>43</td>
</tr>
<tr>
<td>Gorlin syndrome</td>
<td>PTCH</td>
<td>Basal cell carcinomas of the skin, medulloblastomas</td>
<td>44,45</td>
</tr>
<tr>
<td>Neurofibromatosis 1</td>
<td>NF1</td>
<td>Neurofibrosarcomas, pheochromocytomas, optic gliomas</td>
<td>46,47</td>
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<tr>
<td>Neurofibromatosis 2</td>
<td>NF2/merlin</td>
<td>Vestibular schwannomas</td>
<td>48</td>
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<tr>
<td>Tuberous sclerosis complex</td>
<td>TSC1, TSC2</td>
<td>Myocardial rhabdomyoma, multiple bilateral renal angiomyolipoma, ependymoma, renal cancer, giant cell astrocytoma</td>
<td>49</td>
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<tr>
<td>Von Hippel-Lindau disease</td>
<td>pVHL</td>
<td>Hemangioblastomas of the brain, retina, and spinal cord; renal cell cancer, pheochromocytoma</td>
<td>NCR ††</td>
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<tr>
<td>Retinoblastoma</td>
<td>RB1</td>
<td>Retinoblastoma, osteosarcoma, soft tissue sarcomas, melanoma</td>
<td>50,51</td>
</tr>
<tr>
<td>Multiple endocrine neoplasia type 2A</td>
<td>RET</td>
<td>Medullary thyroid cancers, pheochromocytoma, parathyroid hyperplasia</td>
<td>52</td>
</tr>
<tr>
<td>Rhabdoid tumors</td>
<td>hSNF5</td>
<td>Rhabdoid tumors of the central nervous system</td>
<td>NCR</td>
</tr>
<tr>
<td>Breast ovarian cancer syndrome</td>
<td>BRCA1, BRCA2</td>
<td>Breast cancer, ovarian cancer, prostate cancer, pancreatic cancer</td>
<td>NCR †</td>
</tr>
</tbody>
</table>

Abbreviations: PND, prenatal diagnosis; PGD, preimplantation genetic diagnosis; NCR, no case reported.

\*M.R. Hughes, personal communication, October 2005.
\*S.A. Gitlin, personal communication, May 2006
\*S. Munné, personal communication, May 2006

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cololectic cancer. The possible clinical implications of being a carrier of a single MYH mutation remain unclear, however. Perhaps because this syndrome was relatively recently described, no case of prenatal diagnosis has been reported.

**Dominant Disorders**

Li-Fraumeni syndrome (LFS) is caused by inherited TP53 mutations and is associated with multiple early-onset primary malignant tumors in children, including sarcomas, adrenal carcinomas, leukemias, and brain tumors, as well as early-onset breast cancer and other tumors. Genetic counseling and prenatal testing have been performed for LFS, and may offer psychological benefit to families at high-risk for the disease by reducing uncertainty. Familial adenomatous polyposis (FAP) is associated with early onset colorectal neoplasia. In a reported case, a male proband at the time of his test result disclosure elected to have prophylactic colectomy at age 15 and requested sterilization. After genetic counseling, he deferred sterilization, and he and his partner later opted for prenatal diagnosis of his inherited APC mutation. Gorlin syndrome is characterized by craniofacial and skeletal abnormalities as well as predisposition to numerous basal cell carcinomas of the skin, medulloblastomas, and jaw cysts. Definitive prenatal diagnosis has been documented in several affected families. Prenatal genetic diagnosis has also been performed for neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), tuberous sclerosis, retinoblastoma (RB), and multiple endocrine neoplasia type 2A. Hereditary nonpolyposis colorectal cancer (HNPCC) is caused by inherited mutations in mismatch repair (MMR) genes, and is associated with a significantly increased risk for colorectal, uterine, and other malignancies. Rarely, individuals who have inherited two MMR mutations have been described with unique, clinical features including childhood onset leukemia, lymphoma, glioblastoma, and colorectal cancer. To date, there are no case reports of prenatal diagnosis performed for autosomal recessive HNPCC, nor for the more common, dominant form of HNPCC associated with adult-onset malignancies. There have also been no reports of prenatal diagnosis for predisposition to breast and ovarian cancer due to mutations in BRCA1 or BRCA2.

**PGD for Cancer Predisposition Syndromes**

**Recessive Disorders**

PGD has been used to identify human leukocyte antigen (HLA)-matched siblings for children born with bone marrow disorders such as FA who require stem-cell transplantation. PGD has resulted in an unaffected HLA-matched brother and a subsequent successful transplant using umbilical cord blood. Nine couples with children affected by acute lymphoid leukemia, acute myeloid leukemia, or Blackfan-Diamond syndrome underwent PGD selection of HLA-matched siblings resulting in five live births. PGD was performed for Wiskott-Aldrich syndrome in two separate cases, neither of which resulted in clinical pregnancy. PGD has also been carried out for AT.

**Dominant Disorders**

PGD has been performed for two families with LFS, one with a paternally derived and the other with a maternally derived TP53 mutation. In the first case, the carrier was a 38-year-old male who, at age 2 years, was diagnosed with rhabdomyosarcoma of the right shoulder. At 31 years of age, he was also diagnosed with high-grade leiomyosarcoma of the bladder. The couple already had one child who has a 50% risk for LFS. They were highly motivated to document a TP53 germ-line mutation to be referred for PGD. In the second family in this report, the carrier was a 39-year-old female affected with LFS. At the age of 30 years, she was diagnosed with breast cancer and underwent bilateral mastectomy. The patient also underwent surgery for thyroid cystoadenocarcinoma. During PGD, blastomeres were tested for the paternally derived mutation in the first case, and polar body testing was performed for the maternally derived mutation in the case of the second couple. The transfer of unaffected embryos resulted in a singleton pregnancy in both cases. In the first couple, initially seen at the center of one of the authors, the parents have thus far elected not to test their first naturally conceived child for the paternal TP53 mutation.

In the first reported case of PGD for FAP, a 34-year-old patient needed IVF to conceive because a previous colectomy had resulted in the blockage of her fallopian tubes. During PGD, of 10 oocytes retrieved, four were fertilized and biopsied. Subsequently, two blastomeres were biopsied from each of the four embryos to prevent a misdiagnosis caused by allele dropout. Only one embryo was unaffected, but when implanted did not result in pregnancy. PGD for FAP resulting in a live singleton birth has since been successful using polar body analysis for a couple with a maternally derived mutation in the APC gene. Although not reported in peer-reviewed literature, PGD has been successfully performed for HNPCC. A couple in which the father was affected by HNPCC, carrying a mutation in MSH2, participated in PGD, resulting in the delivery of a healthy baby at one center, and single-cell genotyping for at least a dozen other cases of PGD for HNPCC have been performed at another laboratory (M.R. Hughes, personal communication, October 2005). PGD has been carried out for NF1 and NF2, in three separate cases. In the first, PGD was utilized for a couple with a paternally derived NF2 mutation. The 27-year-old male patient had a family history of NF2, and presented with a meningioma of the brain and a schwannoma of the dorsal roots of the spinal cord. Pregnancy did not result in a live-born child for this family. In the other cases, PGD was performed for two couples, one with a maternally derived NF1 mutation, and the other with a paternally derived NF2 mutation. Unaffected embryos were transferred, resulting in a stillbirth in the case of the second couple, and a singleton pregnancy in the case of the third. Another PGD cycle was performed for the second couple, resulting in a twin pregnancy.

PGD has been performed for a couple at risk for producing a child with a paternally derived Von Hippel Lindau (VHL) syndrome mutation. Three PGD cycles were required, resulting in a live, unaffected, singleton birth.

PGD for RB was accomplished in four documented cases to date. In the first case, a maternally derived RB1 mutation was analyzed by polar body analysis using linked markers, but transfer of this embryo did not result in a clinical pregnancy. In a second case, PGD using informative microsatellite markers identified an unaffected embryo, but again, transfer did not result in a clinical pregnancy. In a third case, a 33-year-old male proband was affected with bilateral retinoblastoma, treated with bilateral external beam radiotherapy, chemotherapy, and light coagulation treatments. The couple had a daughter with bilateral RB who developed a brain tumor when she was 2 years old. PGD was carried out for this couple, resulting in the first report of an unaffected live birth after PGD for RB. Subsequently, another unaffected live birth
was reported following PGD for a couple who had terminated three consecutive, affected pregnancies after prenatal diagnosis for RB.70

Mutations of the hSNF5 gene, which lead to sporadic rhabdoid tumors of the CNS, are extremely rare, and have incomplete penetrance. In the first case of PGD for an hSNF5 mutation carrier, PGD was performed for a couple seeking to prevent the birth of a second child with a posterior fossa brain tumor. In this instance, the mutation was maternal, yet the mother was unaffected. However, her daughter, who had inherited the mutation, presented with a brain tumor. In this report, unaffected embryos were transferred, resulting in a successful singleton pregnancy.65

Prenatal and preimplantation genetic testing for hereditary breast and ovarian cancer (BRCA1 and BRCA2) have not been reported in the literature. However, more than one dozen embryo transfers utilizing PGD for BRCA mutation carriers have been carried out at seven IVF centers in the United States, with single-cell genotyping performed at the same laboratory (M.R. Hughes, personal communication, October 2005). Additional PGD cases are underway for three families with BRCA2 mutations (S. Munné, personal communication, May 2006). An ongoing study at University College London (London, United Kingdom) is evaluating interest in PGD among female BRCA mutation carriers. Once the study is completed, a protocol may be developed to offer PGD for BRCA mutation carriers.71 In the spring of 2006, the United Kingdom’s regulatory authority, the Human Fertility and Regulatory Authority, approved PGD for BRCA mutation carriers.

PROFESSIONAL AND PUBLIC POLICY OPINIONS REGARDING ASSISTED REPRODUCTIVE TECHNOLOGIES

Professional societies are active participants in discussing the regulation of PGD and other assisted reproductive technologies. Although the American Medical Association’s (AMA’s) Code of Medical Ethics finds the use of prenatal genetic testing generally acceptable for individuals at “elevated risk of fetal genetic disorder,” the AMA states that “selection to avoid a genetic disease may not always be appropriate, depending on factors such as the severity of the disease, the probability of its occurrence, the age at onset, and the time of gestation at which selection would occur”72; similar positions have been taken by the ethics committee of the American Society of Reproductive Medicine,73 as well as by European medical ethics societies.74-76

The United States President’s Council on Bioethics called for federally funded comprehensive studies on the effects of reproductive genetics practices on “children born with their aid,” and the panel strongly recommended state and federal oversight and monitoring as well as the development of self-imposed ethical boundaries by practitioners.77 To date, comprehensive studies of the outcomes of PGD-assisted births in the United States have not yet been funded.78

DISCUSSION

Health care providers, including oncologists involved in the genetic diagnosis of cancer predisposition syndromes, are commonly asked about strategies to decrease the impact of these syndromes on patients and their families. Constituting an available, albeit not widely known, reproductive option for families affected by hereditary cancer, PGD has already been performed for all of the major familial cancer syndromes, and has been used to create so-called savior siblings who are HLA-matched to children with pediatric cancers who are in need of stem-cell transplantation.

For the practicing oncologist, the most immediate challenge relates to the common syndromes of predisposition to breast and colon cancer. Although cited in a bioethical policy report as an example of a technology that is readily available,79 preimplantation genetic testing for syndromes of breast and colon cancer predisposition has not been incorporated into common practice. Since PGD is available and has been performed for families affected by other cancer syndromes (Table 1), why have so few women in the United States or elsewhere undergone PGD to select, for example, a BRCA wild-type embryo—fully a decade after the cloning of the BRCA genes? Several potential explanations emerge, and may guide oncologists and other health professionals considering whether and how these reproductive options should be discussed with their patients.

The first issue relates to the age at onset of the disorder. For the childhood onset syndromes, such as LFS and RB, the rationale for options such as PGD seems more immediate and compelling than for adult-onset syndromes of common cancer predisposition. In addition, these childhood syndromes are generally of much higher penetrance (virtually 100% of mutation carriers will get cancer), compared with the common adult-onset syndromes, in which penetrance can be as low as 40% to 50%. A third consideration stems from the associated means to decrease genetically acquired cancer risk. Risk-reducing surgeries and intensified surveillance are much better established for the adult-onset syndromes than for most of the childhood syndromes, raising further questions about the need for PGD in these settings. An additional variable in this equation is the extent of contact of the family with specialists. In the case of the rare pediatric syndromes, the family may actually have greater contact with specialists more extensively familiar with assisted reproductive options, thus increasing both access to and acceptance of these options. Factoring in to all of these considerations is the psychological aspect; did family members die prematurely or require care from the person considering PGD, or were only distant relatives affected, and were family members treated successfully without serious sequelae?79

Although each of the aforementioned considerations may help explain the limited uptake of assisted reproductive technologies for cancer syndromes, other more pragmatic considerations must also be taken into account. First, reproductive-age women at risk may simply be unaware of this option. In the United States, genetic counselors are generally the providers of information regarding reproductive planning. Oncologists may simply not be aware of or prepared to initiate such discussions with young individuals at hereditary risk for cancer. Research studies underway in the United Kingdom and elsewhere will resolve the question of the level of awareness and attitudes of reproductive-age women.80 Secondly, the availability of these technologies is still restricted to larger referral centers. However, the availability of PGD is increasing as hundreds of IVF centers in the United States and around the world4-8 acquire expertise in micromanipulation of embryos, and gain access to laboratories to whom specimens can be sent for single-cell genotyping.

Overarching these medical and pragmatic considerations are ethical concerns. BRCA testing to guide embryo selection may be seen by some as setting the stage for PGD testing for sex selection, or future testing for late-onset multifactorial disorders (eg, depression, obesity)
or even genetic traits (eg, eye or hair color). Although averting the issues surrounding pregnancy termination, the increased use of PGD will result in a renewed debate regarding the status and potential medical or research uses of the 10 to 20 oocytes typically collected, fertilized, and then left unused after the parents’ reproductive plans are fulfilled. Finally, there is the issue of equity. If PGD is available to only the wealthy, this raises the specter of genetic selection according to economic means.

In the midst of this discussion, physicians—including oncologists—may soon find themselves at the leading edge of the application of assisted reproductive technologies for families affected by cancer. Health care practitioners will largely do so in the absence of regulation in this area by such federal agencies as the US Food and Drug Administration, and also absent scientific data supporting the long-term safety and outcomes associated with reproductive technologies. And, as in the circumstances of the duty to warn family members regarding hereditary cancer risks, physicians could potentially be subject to hypothetical liabilities around wrongful birth issues resulting from their perceived failure to inform their patients of the possible application of reproductive technologies. Although the lack of accessibility to and unproven long-term safety of assisted reproduction for cancer syndromes limit such claims at the present time, wrongful-life suits have already been filed in cases in which diagnostic reproductive technologies have failed.

Just as oncologists and other health care practitioners have begun to utilize genetic testing to more effectively manage familial cancer syndromes, they must now increase their awareness of the reproductive options available to their patients with hereditary cancers. At present, the uptake of assisted reproductive technologies in the setting of hereditary cancer is limited. However, there is a clearly perceived need for ethical, regulatory, and professional practice guidelines regarding assisted reproduction in the setting of cancer predisposition syndromes. Physicians providing care to families affected by cancer can contribute to the development of these guidelines and to the responsible translation of new reproductive technologies to the practice of preventive medicine.

**REFERENCES**

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70. Tistone C, UK clinicians to screen embryos for BRCA mutations. Lancet Oncol 6:358, 2005


Acknowledgment
We thank Sara Spencer for her research assistance.

Appendix

Table A1. PGD Centers in the United States Listed on www.genetests.com

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Location</th>
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<tbody>
<tr>
<td>Baylor College of Medicine Preimplantation Genetics Laboratory</td>
<td>Houston, TX</td>
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<tr>
<td>Brigham and Women’s Hospital BVH Cytogenetics Laboratory</td>
<td>Boston, MA</td>
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<tr>
<td>Eastern Virginia Medical School Jones Institute for Reproductive Medicine</td>
<td>Norfolk, VA</td>
</tr>
<tr>
<td>Fertility Center and Applied Genetics of Florida</td>
<td>Sarasota, FL</td>
</tr>
<tr>
<td>Froedtert Hospital and Medical College of Wisconsin, Reproductive Medicine</td>
<td>Milwaukee, WI</td>
</tr>
<tr>
<td>Genetics &amp; IVF Institute Preimplantation Diagnosis Program</td>
<td>Fairfax, VA</td>
</tr>
<tr>
<td>Genomics Center at Samaritan Genesis Genetics Institute</td>
<td>Detroit, MI</td>
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<tr>
<td>Genzyme Genetics</td>
<td>Monrovia, CA</td>
</tr>
<tr>
<td>Cytogenetics Laboratory/Molecular Diagnostic Laboratory</td>
<td>Westborough, MA</td>
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<td>Mayo Clinic Fertility Testing Laboratory</td>
<td>Rochester, MN</td>
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<td>Reproductive Genetics Institute</td>
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<td>Reprogenetics</td>
<td>West Orange, NJ/San Francisco, CA</td>
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<tr>
<td>Wake Forest University School of Medicine, Section on Medical Genetics</td>
<td>Winston-Salem, NC</td>
</tr>
<tr>
<td>Weill Medical College of Cornell University Preimplantation Genetics Laborat</td>
<td>New York, NY</td>
</tr>
</tbody>
</table>

Authors’ Disclosures of Potential Conflicts of Interest
The authors indicated no potential conflicts of interest.

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Conception and design: Kenneth Offit, Shelly Cummings
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GLOSSARY

Dominant: A dominant gene refers to the allele that causes a phenotype that is seen in a heterozygous genotype.

Homozygosity: The presence of the same alleles at a particular gene locus on homologous chromosomes.

IVF (in vitro fertilization): A procedure in which fertilization occurs outside of the body. The embryos are either placed in a woman’s uterus or stored for future use.

MMR (mismatch repair genes): Mismatch repair genes recognize and correct errors in DNA replication leading to single base-pair mismatches or insertions/deletions in small repetitive tracts of DNA known as microsatellites.

Phenotype: The overall appearance of an organism, or the observable expression of a specific trait, determined by its genotype and environmental factors.

PGD (preimplantation genetic diagnosis): A method used to identify a disease before an embryo is implanted in the uterus.

PND (prenatal diagnosis): A method used to identify a disease while a fetus is in utero.

Recessive: A trait that is expressed only when the determining allele is present in the homozygous condition.