Point32Health, parent company of
Harvard Pilgrim Health Care & Tufts Health Plan
ETHICS ADVISORY GROUP (EAG) Deliberation

Deliberation Report
Insurance Coverage of Pre-implantation Genetic Testing – Ethical Considerations
September 11, 2023

Purpose
To seek input from the multi-stakeholder Ethics Advisory Group (EAG) on health plan considerations for coverage of pre-implantation genetic testing for hereditary cancers.

Customers for the Ethics Advisory Group and Expert Guests
The Point32Health customer for the EAG meeting were Desiree Otenti, MSN, MPH, Vice President of Quality and Medical Policy. Jochen K Lennerz, MD, PhD, Associate Professor of Pathology, Harvard Medical School and Associate Pathologist, Medical Director, Center for Integrated Diagnostics, Massachusetts General Hospital, offered expert remarks.

Background
Overview
Most prospective parents desire healthy children. When parents seek to decrease the risk of inherited diseases in their children, they may opt for in vitro fertilization (IVF) (even though they are not infertile) followed by genetic testing and selection of embryos prior to transfer of an embryo into the uterus. *Preimplantation* genetic testing (PGT) comprises a group of genetic assays that are used to evaluate embryos before transfer to the uterus.[1,2] As reproductive technologies advance and the number of genetic tests continues to grow, use of IVF and PGT in the US increase rapidly.[3,4,5,6]

Brief history, definitions, and uses of PGT
PGT dates to 1989 as an alternative to *prenatal* genetic testing during pregnancy.[7] When prenatal genetic testing identifies a genetic disease, termination of pregnancy is needed to avoid having an affected child. PGT was originally designed to identify in embryos genetic dispositions that would lead to severe, untreatable, or life-threatening childhood onset conditions in an affected offspring.[8] Individuals or couples at risk of transmitting certain genetic factors may use PGT to select an embryo without the genes for the respective disease to avoid passing on the genes to the next generation. PGT involves undergoing IVF (requiring ovarian stimulation with hormone treatment, egg retrieval, and in-vitro egg fertilization), genetic testing of the embryos, and transfer of an unaffected embryo into the uterus for implantation.

Preimplantation genetic testing-monogenic (PGT-M) examines embryos for single-gene disorders (e.g., spinal muscular atrophy, cystic fibrosis, Huntington's disease) or hereditary cancer syndromes (e.g., hereditary breast and ovarian cancer, Lynch syndrome).[9] In addition to selecting *against* fatal or severe genetic childhood-onset diseases, PGT-M is used for the following other main purposes in the US:[7] by parents of a sick child needing a stem cell transplant to give birth to a child with genetically matching tissue who could serve as a "savior sibling" for the sick child; by prospective parents with a particular genetic trait to select *for* the trait (e.g., deafness, dwarfism); for non-medical sex-selection; and for selection against a wide and increasing range of adult-onset diseases.

More recently, some have advocated PGT for polygenic conditions (PGT-P).[10,11,12] Polygenic disorders result from the combined effect of multiple genes across the genome and are influenced by genes and by environmental and nongenetic factors. With PGT-P, polygenic risk scores (PRSs) of the genetic material in the embryo can be determined for various complex polygenic disorders, such as cardiovascular diseases, cancer, or diabetes, as well as for certain quantitative traits, such as height.[13] In the US, PGT-P is commercially available.[14,15]

Preimplantation genetic testing-aneuploidy (PGT-A) is used to select against embryos with extra or missing chromosomes, referred to as aneuploid, to increase the likelihood of implantation, pregnancy, and life birth.[16] PGT-A is outside the scope of the present EAG discussion.

The glossary (page 11ff) lists definitions of selected terms used in discussions of PGT.

Benefits and risks of PGT

PGT may reduce the risk of passing certain inherited conditions to the next generation. Different from traditional prenatal diagnosis, PGT avoids termination of pregnancy and the physical and emotional burdens associated therewith. However, IVF and PGT carry risks including lower chances of pregnancy and live birth, miscarriage, probability of a misdiagnosis (both false positive and false negative), the possibility that some embryos remain undiagnosed or that all could be affected.[17] There is also a risk of psychological burden induced by a difficult decision between choosing not to transmit a serious hereditary predisposition by undergoing IVF and PGT and potentially diminishing chances of childbearing associated with these procedures.[18]

Ethical questions raised by PGT

PGT raises provocative philosophical and ethical questions about the definition of disease and disability, what life is worth living, "designer babies" and eugenics, the rights of parents to determine the genetic makeup of their offspring and the rights of governments and others to restrict those.[1] What is seen as a 'serious enough' condition to screen against and how far can and should selection be allowed to go, and who should decide this?[13] What are impacts of selection on the genetic makeup of future generations and on society.[19,20]

A review of 38 guidance documents published by advisory committees at national, European, and global levels found PGT ethically acceptable for serious or severe familial conditions associated with suffering.[20] The documents state that "relevant factors for appropriateness of [PGT-M] are severity, lack of treatment options, age of onset, subjective dimensions of suffering, penetrance, and risk of developing a condition".[13] The review found "little room for ethical acceptability of PGT-P"; however, it states that "local contexts could be more lenient, eg, in contexts in which PGT is offered in a free-market approach".[13] A review of studies of the views of health care professionals on the scope of PGT identified similar concerns.[20] Professionals "highlight tensions between respecting patients' autonomy and the professional's role in limiting PGT. […] These tensions emphasize that while expanding the scope of PGT can promote patients' reproductive autonomy, it can also lead to an increased genetic responsibility and reproductive 'burden'."[20]

Regulation of PGT

Unlike in many European countries, PGT is not regulated in the United States.[7,21] As a result, under the framework of reproductive liberty, PGT may be used for any condition for which genetic testing is available, at the discretion of fertility specialists and their patients.[9] This status quo complicates

discussions of ethical issues and coverage questions.

Business of PGT

PGT in the United States is part of a complex business environment.[22,23,24,25] A few years ago, investors were investing heavily in the fertility industry.[23] One expert investor stated in 2018 that "underlying all of this is another industry that really hasn't even started to be developed, which is to use IVF for what I call preventive gene therapy. In other words, fertile couples who have no difficulty getting pregnant use IVF to lower their risk of having babies with serious diseases."[23] More recently, experts have highlighted a lack of expected profitability of some genetic testing laboratories.[24] They mention the following reasons, intense competition; excessive expenses for sales, marketing, and executive compensation, the inclusion of genetic counseling as part of their testing service, and poor reimbursement from insurance plans and patients; and as a consequence of lower profitability, the loss of highly trained experts including genetic counselors.[25] A "call for action" directed at stakeholders in the field of reproductive medicine states that "[i]f fertility physicians and patient advocates proclaim the importance of genetic counseling services not only for best practices in fertility care, but also for their role in identifying opportunities to prevent disease when desired by patients, insurance companies will be pressured to update their coding standards and reimbursement algorithms".[25]

PGT-M for BRCA gene mutations[26]

This EAG discussion focused on PGT-M for selection against adult-onset diseases, specifically hereditary cancers. Clinicians at one IVF clinic (NYU Fertility Center in New York) reported that testing for the breast cancer-related gene BRCA1 was the most frequently performed genetic test in their clinic between 2010 and 2021 and that the proportion of individuals undergoing PGT-M testing for hereditary cancers doubled between 2018 and 2021.[5]

About 5% to 10% of breast and 10% to 15% of ovarian cancers are hereditary. Most, but not all, hereditary breast cancers are linked to BRCA gene mutations. BRCA1 and BRCA2 are tumor suppressor genes. Mutations in BRCA genes raise a person's risk for getting breast cancer at a young age, and for getting ovarian and other (prostate, pancreatic) cancers. About 1 in every 500 women in the United States has a BRCA1 or BRCA2 gene mutation; individuals with a family history of breast or ovarian cancers and individuals with Ashkenazi Jewish ancestry (1 in 40 women) have higher risks of BRCA mutations.[26]

Not everyone with a BRCA mutation will get breast or ovarian or other cancers. With a BRCA gene mutation, about 50 out of 100 women will get breast cancer by age 70 years old (compared to 7 of 100 women in the general United States population); about 30 of 100 women will get ovarian cancer by age 70 years old (compared to fewer than 1 out of 100 in the general U.S. population).[26] Effective options exist to prevent breast and ovarian cancer in women with BRCA mutations. The most effective option is surgery to remove the breasts (mastectomy) and ovaries and fallopian tubes (salpingo-oophorectomy). Other available, possibly less effective, options include taking medications (such as tamoxifen and raloxifene, and aromatase inhibitors) to lower the chance of developing breast or ovarian cancer. For individuals with BRCA mutations, annual screenings for breast, ovarian, prostate, and pancreatic cancers may be recommended to start at younger ages than for those without the genetic mutation.[26]

Ethical issues in PGT-M for adult-onset conditions

In 2018, the Ethics Committee of the American Society for Reproductive Medicine (ASRM) issued its opinion on PGT-M for adult-onset conditions (see Box below).[27]

Box: Key points of ASRM Ethics Committee opinion on PGT-M for adult-onset conditions[27]

- Preimplantation genetic testing for monogenic disease (PGT-M) for adult-onset conditions is ethically justifiable when the conditions are serious and when there are no known interventions for the conditions, or the available interventions are either inadequately effective or are perceived to be significantly burdensome.
- For conditions that are less serious or of lower penetrance, PGT-M for adult-onset conditions is ethically acceptable as a matter of reproductive liberty.
- Physicians and patients should be aware that much remains unknown about the long-term effects of embryo biopsy on a developing fetus. Though thought to be without serious side effects, PGT-M for adult-onset diseases of less serious or of variable penetrance should be considered only after patients are carefully and thoroughly counseled to weigh the risks of what is unknown about the technology and the biopsy itself against the expected benefit of its use.
- It is important to involve the participation of a genetic counselor knowledgeable about such conditions before patients undertake PGT-M. Physician counseling should also address the patient-specific prognosis for achieving pregnancy and birth, if known, through in vitro fertilization (IVF) with PGT-M.
- If the IVF team is not comfortable transferring embryos that would result in offspring affected by the disease in question, they are not obligated to do so. In such cases, clinics should notify patients prior to starting treatment

ASRM considered arguments in support of PGT-M for serious adult-onset conditions including the "right to reproductive choice on the part of persons who seek to bear children, the medical good of preventing the transmission of genetic disorders, the avoidance of abortion based on the revelation of a genetic disorder through prenatal testing, and potential societal benefits of reducing the overall burden of disease". Arguments against the use of PGT-M included "expense, the questionable value of the medical benefits obtained in light of our inability to predict medical progress over the longer term, the possibility of misdiagnosis, the unknown risks of the procedure, and the possible negative impacts on persons living with the genetic disease or predisposition for the condition".[27] The Ethics Committee acknowledged that "[c]ancer predisposition genes such as BRCA present a unique set of challenges. The current understanding of the complex interactions between DNA and the environment is limited. A woman who carries a BRCA1 gene has an increased risk for the development of breast and ovarian cancer but may never develop cancer for reasons that are not yet understood."[27]

Clinical guidance on PGT-M for carriers of BRCA mutations with and without cancers seems to be limited.[18] A recent European review of clinical data concluded: "Success rates [of life births] seem to be lower in oncologic contexts, with the risk of an altered quality of life due to a heavy psychological burden, induced by choosing not to transmit a serious hereditary predisposition at the potential expense of childbearing, and new heavy treatment protocols following previous cancer treatments. Despite the difficulty to draw conclusions from these studies, which include a limited number of patients, it seems that BRCA related PGT might not be beneficial for some patients, which raises the question of whether or not PGT should be proposed to all BRCA carriers."[18]

In the inter-related complex scientific, regulatory, commercial, clinical, and ethical contexts, clinicians, and patients (and the genetic testing industry) turn to health insurers for coverage of PGT-M for BRCA mutations and other conditions.

Point32Health PGT coverage

The June 5, 2023 medical necessity guideline for members in commercial Tufts Health Plans requires prior authorization for PGT.[28] PGT-M may be covered, among other conditions, when the "Fetus would be at risk for an inherited genetic disorder, as defined below, associated with severe disability and/or premature death". The guideline lists examples of more than 30 such disorders. It excludes from coverage "PGT for hereditary mutations which manifest in adulthood (e.g. BRCA testing)".

Ethical issues in insurance coverage of PGT-M for hereditary cancers

No insurer can or should cover all services that are technically possible. Most commercial insurance coverage hinges on the medical necessity of the service for the enrolled member's covered health condition. Ethical considerations whether available medical technologies should be paid for by health insurers have multiple dimensions. Ethical aspects of PGT coverage are particularly complex.

We can broadly consider ethical questions emerging from responsibilities of the payer to *individual members*, to the *population of members*, and to *society.* A health insurer balances its obligation to cover services consistent with accepted standards of medicine for individual members with its obligation to steward resources for all its members. Is PGT-M for hereditary cancers that may manifest in adulthood medically advisable preventive genomic medicine that provides potential benefits (and risks) for an individual member or possible health benefits for their offspring, or both? If children with increased risk of hereditary cancers develop those cancers at some point in their life, effective screening and treatment modalities are available and covered by insurers now and more will likely be available in the future. To what extent should treatability factor into the decision? Does PGT-M coverage facilitate reproductive autonomy for individual members resulting in selective reproduction by insured members who would be able to access genetic testing including PGT?

It is likely that more educated, wealthier, white members would preferentially access covered PGT services. That is, their reproductive choices would be more likely to affect the next generation. How should differential socio-economic impacts be considered? If PGT is considered preventive genomic medicine, should it be considered preventive care by the responsible federal agencies and therefore eligible for preventive benefits coverage? Would coverage of PGT-M and eventually elimination of serious (or less serious, especially if PGT-P is used in health care) illnesses potentially decrease health care spending and thus make more resources available at the member population and society levels?

Genetics is a relatively new science. Much is not known about how genes interact with one another. By selecting against one gene or one trait, we are likely to also select for or against others that are not yet known to be connected. Therefore, at the population level, if we decrease the prevalence of BRCA mutations, what are unforeseen downstream genetic and health consequences?

What is the moral co-responsibility of the payer with respect to facilitating access to technologies that affect the wellbeing of future individuals and the genetic make-up of society in the future? How is wellbeing defined? Is it a life without the genetic makeup associated with risks of certain illnesses, is it a life with certain selected traits? And who should answer these questions?

We discuss these and other questions considering a family's trajectory. The case presented was developed by EAG expert guests Dr. Jochen Lennerz and his colleague Ula Green.

Selected Related Prior Ethics Advisory Group (EAG) Deliberations

At least 5 past EAG deliberations have addressed topics related to the present discussion.[a] Relevant suggestions made by EAG participants in past discussions include:

- In 2005, the EAG mentioned that "the current wild west of entrepreneurial personal genomic services" should be regulated and noted the health plan's role in *contributing to public policy debate*.
- In 2008, the EAG noted that genetic/genomic developments can improve patient outcomes, reduce overall risk, and make better use of health plan funds and it highlighted misunderstanding of the meaning of genetic and genomic information. Education on genetics/genomics was considered consistent with the health plan's "brand" and internal *values of educating members and other constituents* and fostering collaboration in managing complex areas of health care.
- In 2019, the EAG discussed *compassion as a key value* and the default frame for direct and indirect actions of a health plan. Compassionate responses to an individual's suffering must consider a health plan's responsibilities to *fairness, equity, and fiscal stewardship within the complex health system*. EAG participants suggested that simplifying health plan policies and procedures as permitted by law and accreditors, combined with support for members and others in navigating the increasingly complex health system, reflects a plan's focus on compassion. They affirmed that a well-documented and publicized focus on compassion is an important aspect of the reputation of the organization.
- In 2023, the EAG underscored a need for and responsibility of the health plan to *engage with all its stakeholders proactively and visibly about the trade-offs* that are required, locally and nationally, by increasing spending. Communication should include *a focus on equity* and will require a long-term strategy to be effective.
- In 2023, the EAG suggested that *coverage expansion* should be implemented prudently, in a step-change fashion, and following fair priority-setting processes. *Fair priority setting* requires deliberation by all 'fair-minded' stakeholders (including those affected by the decision), transparency of the decision and reasons behind it, and mechanisms through which stakeholders can appeal a decision and it can be revised.

Questions for the Point32Health Ethics Advisory Group Deliberation

On September 11, 2023, the Ethics Advisory Group was asked to reflect on the following questions:

1. Which principles should health plan leaders consider in their decisions about coverage of pre-implantation genetic testing for mutations that increase the risk of hereditary cancers (PGT-M)?
2. Pre-implantation genetic testing is available for many more conditions that are results of combinations of genetic, environmental, and other factors, that have less severe impacts on most patients' lives, and for which treatments exist now and more treatments will likely exist in the future. Which principles should health plan leaders be prepared to consider in decisions about coverage of pre-implantation genetic testing (PGT-P) for diseases like cardiovascular diseases and diabetes in the future?

[a] 2005, Values Framework for New Technologies; 2008, Anticipating the Ethical Challenges of Genomic Medicine; 2019, Compassion in Health Care - The Roles of a Health Plan; 2023, Affordability of New Therapies - Principles for Health Plan Communication; 2023, Fertility Care - Considerations for Health Plans. EAG deliberation reports are available from anita_wagner@hm.harvard.edu.

Summary of the Point32Health Ethics Advisory Group Deliberation
Almost 60 individuals participated in the conversation. The Point32Health customer Desiree Otenti, MSN, MPH, Vice President of Quality and Medical Policy, highlighted the evolution of coverage over time of pre-implantation genetic testing for monogenic diseases (PGT-M). The expert guest Dr. Joe Lennerz explained the validity and accuracy of PGT laboratory procedures.

In the past, PGT-M was used for selecting against embryos with genes that would almost certainly result in single-gene determined diseases that would have caused early childhood death (e.g., spinal muscular atrophy) since no treatments were available. PGT-M is now also used, and covered by Point32Health, to select against embryos with a single gene that would almost certainly cause childhood or adult-onset diseases that are considered severely impacting life (e.g., cystic fibrosis, Huntington's disease). This EAG deliberation focused on ethical principles for considering health plan coverage of PGT-M to select against embryos with genes that would result in a higher risk of (but not almost certainly cause) certain adult-onset cancers (e.g., BRCA-mutated breast and ovarian cancers) than if the embryo did not carry the gene. Early diagnosis and treatments of some of these cancers exist and individuals without the BRCA mutations are still at risk for non-BRCA-mutated breast and other cancers.

PGT-M involves a series of clinical and laboratory procedures. These include: a physician consult, ovarian stimulation with hormones to boost egg production, pelvic ultrasounds, blood tests, hormone triggers, egg retrieval (ultrasound guided, transvaginal, with anesthesia), in vitro fertilization, incubation, embryo culture; biopsy, testing, and freezing of genetically normal embryos; embryo transfer, and pregnancy testing. PGT-M testing, like most medical tests, can yield wrong (false positive and false negative) and uninformative results.

EAG participants considered the case of a family opting for IVF/PGT for conceiving their second child. The 2-part case vignette is presented on page 10. Briefly, the woman carried the BRCA mutation, her mother died of BRCA-mutated breast cancer, and the couple had a BRCA mutation-negative child which they conceived without IVF/PGT (part 1, question 1). They opted to undergo IVF/PGT-M to conceive their second child. Their second child was found to carry the BRCA mutation (part 2, question 2).

EAG poll results

	Question 1 (considering part 1 of the case): Do you think the health plan should cover PGT (and IVF) for the Smith family? (n=43)	Question 2 (considering part 2 of the case): Knowing the evolution of the Smith's trajectory, do you think the health plan should cover PGT (and IVF) for individuals like the Smith family? (n=42)	Question 3: Now please consider the following population-level question: Do you think the health plan should cover PGT-M (and IVF) for every member desiring PGT-M for BRCA mutations? (n=41)
Yes, n (%)	15 (35)	12 (29)	8 (20)
Not sure, n (%)	22 (51)	24 (57)	14 (34)
No, n (%)	6 (14)	6 (14)	19 (46)

Poll results show that more than half of voting EAG participants were not sure whether the health plan should cover IVF/PGT for the couple described in the case. Learning about the false negative test implications, fewer respondents voted for coverage and more respondents indicated that they were not sure. When asked to consider coverage at the member population level, 19/41 (46%) thought that the health plan should not cover PGT-M for every member desiring PGT-M for BRCA mutations.

In discussing these poll results and the broader EAG questions (page 6), EAG participants offered the following reflections:

- Understanding test accuracy and disease risk: No test can be perfect. Some participants suggested that lack of test accuracy would not change their perspective. The discussion also highlighted that individuals are likely to overestimate the predictive validity of tests (including BRCA carrier screening tests) and many people are unlikely to understand disease risk. Test results, perceptions of test accuracy, and assumptions about disease risk will influence individuals' behaviors. For example, individuals who do not carry the BRCA mutation may forego regular mammograms mistakenly assuming that they are not at risk for breast cancers. A 2008 EAG suggestion may still hold: education on genetics remains necessary and consistent with the health plan's value of educating members and other constituents to help manage complex areas of health care.
- Suffering: Prospective parents with known genetic pre-disposition for serious illnesses may experience anxiety and suffering associated with the decision to have children. Suffering may occur for many reasons, including the fear of passing on genes for a serious illness and the responsibility of deciding for or against IVF/PGT. IVF/PGT procedures are also associated with physical and emotional health impacts. EAG participants agreed that individual suffering must be addressed with proper genetic counseling. They also mentioned that IVF/PGT should not be viewed as a treatment for anxiety regarding reproduction, but that psychological counseling should be offered.
- Individual reproductive rights: Several EAG participants voiced the perspective that the health plan should facilitate individuals' decisions to reproduce in the face of a known genetic disposition for BRCA-mutated cancers. Specifically, since the health plan covers BRCA carrier screening for at-risk individuals, the health plan's coverage of IVF/PGT-M would be consistent with giving individuals the choice to act on results from carrier screening by opting for IVF/PGT to seek a child without the mutation.
- Population-level reproductive justice: Without health plan coverage of IVF/PGT-M, only wealthier individuals will be able to afford the cost of IVF/PGT-M and seek eliminating the genetic predisposition from their families. With health plan coverage of IVF/PGT-M, more individuals will be able to do so, but not all. It is an open question whether it is the role of the health plan to contribute to reproductive justice in this way.
- Opportunity costs and health plan financial stewardship: Expansion of population coverage for IVF/PGT-M for hereditary cancers, and possibly other conditions associated with a genetic mutation and lower risk of occurrence, may divert scarce health plan resources from other uses. Opportunity costs could impact members through higher out-of-pocket payments and premiums. EAG participants also noted that a health plan covering PGT-M for hereditary cancers would likely not benefit financially from avoided costs for treatments of those cancers as member populations change over time.
- The following considerations raise additional, challenging societal questions:
    - More gene therapies are increasingly available to treat[29,30] (and potentially cure) some of the childhood onset diseases that formerly resulted in early death and for which PGT-M is currently considered ethically justified.

- PGT use is expanding to seek elimination of genes that carry lower risk of adult-onset, treatable chronic conditions with variable impacts on lives.
- Some parents with certain genetic traits (e.g. deafness or dwarfism) may wish to use PGT-M to select embryos with the same genetic trait.
- PGT decisions invoke concern of eugenics.

What signals does health plan coverage, or denial of coverage, of PGT for different purposes set about "a life worth living"? And what shared responsibility does, and should, the health plan have in societal consequences of PGT? For which conditions (or traits) should a health plan never cover PGT? How should a health plan make sure that members with genetically linked diseases and their families continue to have access to high quality care, regardless of their decision to use IVF/PGT.

- Consistent with published ethical guidance documents,[13] EAG participants suggested the following principles for health plan decisions about PGT-M coverage: *serious familial conditions* associated with *subjective suffering*, *high (to be defined) risk* of developing the condition, and *lack of treatment* options.
- Consistent with published ethical opinion,[9,7] there was also a call for advocacy for regulatory oversight of PGT.

Perspectives shared during this EAG deliberation highlighted again[b] the ethical complexity of decisions payers are increasingly asked to make. Rapid medical technological developments may decrease suffering of some individuals. At the same time, in the US, upstream regulation to protect individuals and society from potential harms of new technologies and payers and society from wasting scarce resources is lacking. Payers should consider efforts to increase equitable access to new technologies in this context.

In summary, in the current context, the EAG deliberation suggested a case-by-case evaluation of coverage of PGT-M to decrease the risk of hereditary cancers. An individual evaluation should require qualified genetic and psychological counseling of the member and consider the severity of a known familial condition, risk of developing the condition, treatment options, and subjective suffering.

This report is respectfully submitted, with gratitude to Point32Health leaders, the expert guest, and all who generously shared their perspectives for making this important and timely Point32Health EAG conversation possible. Thanks also go to Alyssa Halbisen, Kelsey Berry, and Caitlyn Tabor for supporting EAG deliberations.

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[b] See these prior EAG deliberations: 2023, Affordability of New Therapies - Principles for Health Plan Communication; 2023, Fertility Care - Considerations for Health Plans. For reports, please contact awagner@hms.harvard.edu.

Case description (courtesy Jochen Lennerz & Ula Green, Center for Integrated Diagnostics, Massachusetts General Hospital)

Part 1
The Smiths (Monica and Akim), a couple in their early 30s, have a family history of breast cancer. Mrs. Smith's mother and aunt were both diagnosed with breast cancer. Mrs. Smith's mother had a tumultuous cancer course, enduring a long and challenging battle with breast cancer. The Smiths have one six-year-old daughter, Jessica.

Witnessing her mother's struggle and the impact it had on their family has instilled deep concerns in the Smiths about the potential hereditary risks of passing on the BRCA1 gene mutation to their children. Following her mother's diagnosis, Monica learned that she carries a specific BRCA1 gene mutation known to be associated with an increased risk of developing breast and ovarian cancer and that Jessica does not. Concerned about passing on this inherited genetic disease to their future children, the Smiths had abandoned the idea of having another child.

The Smiths had been closely following the journey of their friends, who faced a similar situation and apparently did "a test to select healthy embryos". The Smiths learned that the procedure is called preimplantation genetic testing (or PGT). The Smiths sought information about PGT from a genetic counselor and a reproductive endocrinologist. With new hope to expand their family, they were surprised to learn that their health plan would not cover the costs of IVF and PGT to permit selection and implantation of an embryo that would not harbor the genetic mutation.

Part 2
The Smiths joyfully welcomed a healthy baby girl into their lives. As their second daughter grew older, it became a deeply emotional journey for the Smiths, as they were reminded of the absence of Mrs. Smith's mother, who had unfortunately passed away due to recurrence of her breast cancer. While Monica continues to diligently follow recommendations for breast and ovarian cancer screening, the recent loss of her mother further intensified the Smiths' commitment to proactive healthcare. Their concerns were heightened upon hearing recent news about errors in PGT.

They wanted to ensure their daughter's well-being and health and consulted with their healthcare team and decided to have their second daughter undergo genetic testing. To their dismay, the results of the genetic testing revealed that their second daughter carried the BRCA1 mutation. The news came as a shock to the Smiths, as they had hoped that by utilizing PGT, they could break the cycle of the mutation within their family. The Smiths immediately sought guidance from their genetic counselor and healthcare providers. The team provided them with resources to help them navigate the emotional and practical challenges.

Glossary

Selected terms and definitions

Term	Definition
Amniocentesis	Amniocentesis: a test done by taking fluid from the amniotic sac during pregnancy to test for conditions in the fetus.[1]
Aneuploidy	Having an abnormal number of chromosomes. Types include trisomy, in which there is an extra chromosome, or monosomy, in which a chromosome is missing. Aneuploidy can affect any chromosome, including the sex chromosomes. Down syndrome (trisomy 21) is a common aneuploidy. Others are Patau syndrome (trisomy 13) and Edwards syndrome (trisomy 18).[31]
Blastocyst	The stage of embryo development that occurs 4 to 5 days after fertilization.[31]
BRCA	(BRCA1 and BRCA2) Genes that keep cells from growing too rapidly. Changes in these genes have been linked to an increased risk of breast cancer and ovarian cancer.[31]
Chorionic villus sampling (CVS)	Chorionic villus sampling (CVS): a test done by taking cells from the placenta in early pregnancy to detect genetic conditions in the fetus.[1]
In-vitro fertilization (IVF)	An ART procedure that involves removing eggs from a woman's ovaries and fertilizing them outside her body. The resulting embryos are then transferred into a woman's uterus through the cervix.[32]
Mosaicism	Two or more cell populations with different chromosomal complements present within the same embryo.[2]
Penetrance	Penetrance refers to the likelihood that a clinical condition will occur when a particular genotype is present. For adult-onset diseases, penetrance is usually described by the individual carrier's age, sex, and organ site.[33]
Polygenic risk score	An assessment of the risk of a specific condition based on the collective influence of many genetic variants. These can include variants associated with genes of known function and variants not known to be associated with genes relevant to the condition. Also called PRS.[33]
Pre-implantation genetic diagnosis (PGD)/testing (PGT)	Preimplantation genetic testing (PGT): screening test performed during in vitro fertilization (IVF). There are three types: PGT-M, PGT-SR, and PGT-A, each involving testing of an embryo for certain genetic conditions (such as cystic fibrosis or Down syndrome). This type of testing was formerly called preimplantation genetic diagnosis (PGD).[1]
Preimplantation genetic testing-aneuploidy (PGT-A)	The main purpose of PGT-A is to screen embryos for whole chromosome abnormalities. Before its use, the selection of embryos for transfer was based mainly on morphologic criteria, but many women failed to achieve pregnancy despite transfer of morphologically optimal embryos. Preimplantation genetic testing-aneuploidy was proposed as a way to detect whole chromosome

Term	Definition
	aneuploidy before transfer and thus potentially increase live birth rates and decrease early pregnancy failure rates. The original technique used fluorescence in situ hybridization but was limited to just a few chromosomes. Preimplantation genetic testing-aneuploidy has now expanded to include assessment of all the chromosomes, through various techniques such as array comparative genomic hybridization and next generation sequencing.[2]
Pre-implantation genetic testing-monogenic (PGT-M)	Preimplantation genetic testing-monogenic is used to test for a specific genetic pathogenic variant (mutation) associated with a known diagnosis or known predisposition within a family. Preimplantation genetic testing-monogenic does not test for all single gene disorders at once and will not detect de novo pathogenic variants. This technique examines embryos using either cytogenetic or molecular techniques for (1) single-gene disorders (eg, Huntington disease, cystic fibrosis, fragile X syndrome), including those that are autosomal dominant and recessive or X-linked, or (2) hereditary cancer syndromes (eg, hereditary breast and ovarian cancer, Lynch syndrome). Additionally, preimplantation genetic testing-monogenic can be used to identify human leukocyte antigen-compatible, unaffected embryos gestated with the goal of allowing ill family members to receive compatible bone marrow transplants or cord blood transfusions. Preimplantation genetic testing-monogenic uses only a few cells from the early embryo, usually at the blastocyst stage, and misdiagnosis is possible but rare with modern techniques.[2]
Pre-implantation genetic testing for polygenic disorders (PGT-P)	PGT for a condition or trait (height, eye color) resulting from the combined action of more than one gene. When a condition requires multiple genetic factors to manifest, it is termed a polygenic condition. Many health disorders, such as heart disease and diabetes are polygenic. Most polygenic conditions are also influenced by environmental factors, and these should be considered when assessing an individual's chance of developing a particular condition.[34]
Pre-implantation genetic testing-structural rearrangements (PGT-SR)	To test embryos that are at risk for chromosome gains and losses related to parental structural chromosomal abnormalities (eg translocations, inversions, deletions, and insertions), preimplantation genetic testing-structural rearrangements is used. Genetic counseling and discussion of possible preimplantation genetic testing should be offered when a structural rearrangement is discovered in a parent. At this time, preimplantation genetic testing-structural rearrangements cannot differentiate between an embryo that has a normal karyotype and an embryo that carries a balanced form of the familial chromosome rearrangement. Individuals who carry a balanced chromosome rearrangement involving imprinted genes (eg, 13;14 robertsonian translocation)

Term	Definition
	are at risk for abnormalities related to uniparental disomy, which cannot be excluded by all methods of preimplantation genetic testing analysis. Because of these limitations, and the fact that this testing method uses only a few trophectoderm cells, confirmation of preimplantation genetic testing-structural rearrangements results with CVS or amniocentesis should be offered.[2]
Pre-natal genetic testing	Prenatal genetic testing gives parents-to-be information about whether their fetus has certain genetic disorders. This includes two types of prenatal tests for genetic disorders: prenatal genetic screening tests and prenatal genetic diagnostic tests.[35]
Pre-natal genetic screening	Prenatal genetic screening tests of the pregnant woman's blood and findings from ultrasound exams can screen the fetus for aneuploidy; defects of the brain and spine called neural tube defects (NTDs); and some defects of the abdomen, heart, and facial features.[35]

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