Use of preimplantation genetic testing for monogenic adult-onset conditions: an Ethics Committee opinion

Ethics Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Washington, DC

Preimplantation genetic testing for monogenic diseases for adult-onset conditions is ethically permissible for various conditions, including when the condition is fully penetrant or confers disease predisposition. The Committee strongly recommends that a genetic counselor experienced with both preimplantation genetic testing for monogenic diseases and assisted reproductive technology therapies counsel patients considering such procedures. (Fertil Steril® 2024;122:607–11. ©2024 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: ASRM, ethics, PGT-M, reproductive medicine, reproductive science

KEY POINTS

- Preimplantation genetic testing for monogenic (PGT-M) diseases for adult-onset conditions that are most often fully penetrant or confer disease predisposition is ethically justifiable. Decisions on whether conditions are significantly impactful such that PGT-M is warranted are personal ones that differ among patients, whose autonomy to make such distinctions should be supported as a matter of reproductive liberty.
- Patients considering PGT-M should be carefully and thoroughly counseled by a genetic counselor with expertise in preimplantation genetic testing to understand the risks, benefits, and limitations of PGT-M, as well as to discuss the potential manifestations of the hereditary condition. Consulting medical professionals with expertise in the condition to be tested should be considered in addition to help patients make decisions regarding using PGT-M in these situations.
- Physician counseling should address the patient-specific prognosis for achieving pregnancy through in vitro fertilization treatment when used in conjunction with PGT-M.
- Nondirective counseling is important when considering PGT-M to support patient autonomy.

The use of preimplantation genetic testing for monogenic (PGT-M) diseases for adult-onset conditions that are fully penetrant or confer disease predisposition has been increasing steadily in the United States (1). Comprehensive counseling by a genetic counselor knowledgeable in assisted reproductive technology therapies, PGT, and the hereditary condition being tested is critical to ensure that patients are adequately informed before determining their course of action. Prenatal diagnostic testing via chorionic villus sampling or amniocentesis to confirm the results obtained with PGT-M, or as an alternative to PGT-M, should also be discussed with individuals as part of their prenatal genetic counseling. Some reproductive decisions, including termination of pregnancy, may not be available to patients depending on the state in which they reside. Such restrictions should be included in preconceptual counseling regarding reproductive options.

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Initially, PGT-M was developed to identify embryos resulting from in vitro fertilization (IVF) therapy cycles that carried genes for serious childhood-onset diseases. Preimplantation genetic testing for monogenic diseases has been used recently for adult-onset single-gene disorders and disease predispositions (1). Examples include diseases that are not always but most often fully penetrant (e.g., Huntington disease and polycystic kidney disease) and genes that indicate a predisposition for cancer (e.g., *BRCA1* and *BRCA2* gene variants) (2–7). Although Huntington disease is an autosomal dominant condition that is uniformly fatal, the age of onset varies with the pathogenic variant. In

contrast, for cancer syndromes such as *BRCA1* or *BRCA2-associated* hereditary breast and ovarian cancer, the presence of the identified gene variant(s) does not predict with certainty that an individual will ever develop the disease but significantly increases the lifetime risks for associated cancers. Moreover, some conditions can be treated successfully and may not be ultimately fatal or significantly affect the quality of life (8). For other conditions, successful treatments may be developed over time to prevent or treat the conditions for which the offspring are at risk. The use of PGT-M for serious adult-onset conditions thus raises challenging policy and ethical questions, given what is known about the human genome, disease etiology, the pace of medical progress, and embryo biopsy procedures. This includes questions of whether and how the role of commercial laboratories in developing new testing applications may impact prospective patients' choices regarding what tests may be accessible for use. In addition, it calls for acknowledging that the seriousness of a condition may be based on individual judgment, which is often dependent on a person's values, beliefs, and lived experience. Patients should be supported as they determine whether they wish to undergo PGT-M for a given condition as a matter of respect for reproductive autonomy. **As of the publication of this article**, testing for multifactorial diseases and/or the use of PGT-P (preimplantation testing for polygenic conditions) and polygenic risk score assessement for embryo selection remains investigational and should not be offered outside of research protocols (2, 9).

ETHICAL ANALYSIS

Overview

Arguments offered in support of PGT-M for serious adult-onset conditions include 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 on the basis of revelation of a genetic disorder through prenatal testing, and societal benefits of reducing the overall burden of disease. Arguments advanced against the use of PGT-M include 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, and the potential risks of IVF therapy as well as embryo biopsy. Furthermore, the use of PGT-M may have negative impacts on persons living with the genetic disease or predisposition for the condition by calling into question the value of their lives and decreasing funding of research when the disease or predisposition becomes less prevalent in the population.

Arguments in favor of PGT-M for adult-onset conditions

The goal of preventing serious disease supports using PGT-M for adult-onset conditions that are most often fully penetrant or confer disease predisposition. Preimplantation genetic testing for monogenic diseases is an effective intervention to identify these genetic variants (2). Prospective parents may wish to try to avoid the possibility that their offspring will inherit the condition or predisposition of concern. The potential benefit to society is also to avoid the high costs of long-term treatment of severe and/or chronic diseases (10).

In the case of adult-onset diseases, prospective parents may have many reasons for choosing PGT-M. Reproductive liberty is an important, albeit not absolute, right. Prospective parents may wish to avoid the lifelong concern caused by the chance that their children may develop adult-onset health-affecting conditions that have limited or highly burdensome treatments or may shorten their lifespan. Professional organizations such as the American Academy of Pediatrics currently recommend that genetic testing of children for adult-onset conditions for which interventions are unavailable is inappropriate until children reach 18 years of age and adulthood (11–13). This argument is based on the idea that the child has the right to an open future that is not burdened with the knowledge of a genetic condition. Critics have argued that this recommendation against testing fails to understand emerging autonomy and to appreciate the harms that may be associated with uncertainty (14), yet the recommendation was reviewed in 2013 (11). In the case of PGT-M, the concept of an open future does not readily apply.

With some late-onset conditions, testing may be medically indicated before the child reaches adulthood. For example, autosomal dominant polycystic kidney disease (ADPKD) results in a progressive decline in kidney function, with kidney failure tending to occur in middle age. Children with ADPKD may not have any symptoms during childhood but require interval blood pressure assessment and renal ultrasonography beginning in childhood to monitor for early signs of kidney damage.

Finally, cost considerations also support the reproductive liberty to choose PGT-M in cases of diseases that are most often fully penetrant or confer disease predisposition. This is particularly relevant given the lifetime cost of health care for chronic medical conditions. With PGT-M, the expenses are borne at the outset; the costs of managing late-onset conditions may be significantly greater by comparison. However, the costs of IVF therapy with PGT-M should not be discounted. These are expensive procedures with no certainty of live birth. Currently, IVF therapy with PGT-M for adult-onset conditions may not be covered by insurance, and access to care is often limited. Efforts should be made to equitably increase access to this technology for those who may benefit from it.

Patients with a genetic condition often require repeated testing and treatment, often from early adulthood or beyond. For example, the financial and public health burdens of ADPKD include lost wages as well as long-term medical treatment (15). Those with disease predispositions often need increased screening, which confers costs on themselves and increases burdens on the health care system. They may also opt for prophylactic procedures such as mastectomy or oophorectomy in the case of a *BRCA* variant that confers an increased risk for the development of cancer. The psychological impact of these diseases should also be considered, because many individuals who carry these genetically inherited conditions must live with the ongoing burden of

fear and concern about the development of disease. Individuals whose embryos are undergoing PGT-M for adult-onset diseases such as Huntington disease may also request that their own carrier status not be disclosed to them. It is ethically acceptable to honor such requests, but this practice remains controversial (16, 17).

Arguments against PGT-M for adult-onset conditions

There are ethical reasons against using PGT-M for adult-onset conditions that are fully penetrant or confer disease predisposition. It is impossible to predict whether effective treatment modalities will be available before the manifestation of identified conditions by the time the offspring reach adulthood. Individuals with the disease-causing genetic variant may live healthy lives for several decades before a disease becomes an active concern in adulthood. Moreover, some of these genes may have variable expressivity or reduced penetrance, manifesting as a much milder form of illness than anticipated or perhaps never expressing illness at all, as in the case of some pathogenic variants that increase the lifetime risk of cancer. Genes that indicate a predisposition to cancer, such as *BRCA1* and *BRCA2*, present unique challenges. The current understanding of the complex interactions between DNA and the environment is limited. A woman who carries a *BRCA1* or *BRCA2* pathogenic variant has an increased lifetime risk of developing breast and/or ovarian cancer but may never develop these cancers for reasons that are not yet fully understood (18).

Critics of PGT-M also argue that using the procedure for embryo selection risks devaluing certain lives (19). They contend that PGT-M can potentially send a negative message regarding the value of those individuals living with the disease, including those who have the mutation for the disease but have not yet developed a physical manifestation of the syndrome (20).

SUMMARY

After careful review and consideration, the Committee concludes, on the basis of the above arguments, that PGT-M for adult-onset conditions that are most often fully penetrant or confer disease predisposition is ethically justified. Considerations including patient autonomy and the importance of supporting reproductive liberty dictate that decisions regarding the use of PGT-M in these situations should be made by patients as they consider the risk of disease development, the role of disease severity, and the age of onset. The complexity of the scientific, psychological, and social issues involved in this arena compels the Committee to strongly recommend that an experienced preimplantation genetic testing genetic counselor with knowledge about both the condition and assisted reproductive technology treatment play a significant role in the counseling of prospective patients considering using PGT-M for adult-onset conditions. Counseling from medical professionals with expertise in the condition should also be considered as appropriate.

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REFERENCES

1. Chang J, Boulet SL, Jeng G, Flowers L, Kissin DM. Outcomes of in vitro fertilization with preimplantation genetic diagnosis: an analysis of the United States assisted reproductive technology surveillance data, 2011-2012. Fertil Steril 2016;105:394–400.
2. Practice Committee and Genetic Counseling Professional Group of the American Society for Reproductive Medicine. Indications and management of preimplantation genetic testing for monogenic conditions: a committee opinion. Fertil Steril 2003;120:61–71.
3. BBC News. Embryos to be screened for squint. Available at: http://news.bbc.co.uk/2/hi/health/6634015.stm. Accessed November 23, 2016.
4. Wang CW, Hui EC. Ethical, legal and social implications of prenatal and preimplantation genetic testing for cancer susceptibility. Reprod Biomed Online 2009;19(Suppl 2):23–33.
5. Human Fertilisation & Embryology Authority (UK). Approved PGT-M and PTT conditions. Human Fertilisation & Embryology Authority. Available at: https://www.hfea.gov.uk/treatments/embryo-testing-and-treatments-for-disease/approved-pgt-m-and-ptt-conditions/. Accessed November 23, 2016.
6. Gigarel N, Frydman N, Burlet P, Kerbrat V, Tachdjian G, Fanchin R, et al. Preimplantation genetic diagnosis for autosomal recessive polycystic kidney disease. Reprod Biomed Online 2008;16:152–8.
7. Bostwick B, Van den Veyver IB, Sutton VR. Focal dermal hypoplasia. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., eds. GeneReviews. Seattle University of Washington; 2008:1993–2016.
8. Metcalfe K, Lynch HT, Foulkes WD, Tung N, Kim-Sing C, Olopade OI, et al. Effect of Oophorectomy on survival after breast cancer in BRCA1 and BRCA2 mutation carriers. JAMA Oncol 2015;1:306–13.
9. Abu-El-Haija A, Reddi HV, Wand H, Rose NC, Mori M, Qian E, et al. The clinical application of polygenic risk scores: A points to consider statement of

the American College of Medical Genetics and Genomics (ACMG). Genet Med 2023;25:100803.
10. Chevreul K, Michel M, Brigham KB, López-Bastida J, Linertová R, Oliva-Moreno J, et al. Social/economic costs and health-related quality of life in patients with cystic fibrosis in Europe. Eur J Health Econ 2016;17(Suppl 1):7–18.
11. Committee on Bioethics. Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee Ethical and policy issues in genetic testing and screening of children. Pediatrics 2013;131:620–2.
12. Kopelman LM. Using the best interest standard to assess whether to test children for untreatable, late-onset genetic disease. J Med Philos 2007;32:375–94.
13. New York State Task Force on Life and the Law, Genetic testing and screening in the age of genomic medicine, Available at: http://educationnewyork.com/files/Genetic%20Testing%20and%20Screening%20in%20the%20Age%20of%20Genomic%20Medicine.pdf. Accessed February 26, 2013.
14. Rhodes R. Genetic testing: is there a right not to know? MCN Am J Matern Child Nurs 2006;31:145.
15. Cavazza M, Kodra Y, Armeni P, De Santis M, López-Bastida J, Linertová R, et al. Social/economic costs and quality of life in patients with haemophilia in Europe. Eur J Health Econ 2016;17(Suppl 1):53–65.
16. Braude PR, De Wert GM, Evers-Kiebooms G, Pettigrew RA, Geraedts JP. Non-disclosure preimplantation genetic diagnosis for Huntington's disease: practical and ethical dilemmas. Prenat Diagn 1998;18:1422–6.
17. Asscher E, Koops BJ. The right not to know and preimplantation genetic diagnosis for Huntington's disease. J Med Ethics 2010;36:30–3.
18. Li S, Silvestri V, Leslie G, Rebbeck TR, Neuhausen SL, Hopper JL, et al. Cancer risks associated with *BRCA1* and *BRCA2* pathogenic variants. J Clin Oncol 2022;40:1529–41.
19. Petersen TS. Just diagnosis? Preimplantation genetic diagnosis and injustices to disabled people. J Med Ethics 2005;31:231–4.
20. Cavazza M, Kodra Y, Armeni P, De Santis M, López-Bastida J, Linertová R, et al, BURQOL-RD Research Network. Social/economic costs and quality of life in patients with haemophilia in Europe. Eur J Health Econ 2016; 17(Suppl 1):53–65.

Uso de pruebas pre implantatorias para la detección de condiciones monogénicas de aparición en la edad adulta: opinión del comité de ética

Las pruebas genéticas pre implantatorias para enfermedades monogénicas que aparecen en la edad adulta son éticamente permitidas por varias condiciones, incluidas cuando la condición tiene penetrancia completa u otorga una predisposición a la enfermedad. El comité recomienda fuertemente que un consejero experimentado en genética tanto en pruebas genéticas pre implantatorias para enfermedades monogénicas y en terapias tecnológicas de reproducción asistida asesore a los pacientes que están considerando tales procedimientos.