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REVIEW

Preimplantation Genetic Testing in the 21st Century: Uncharted Territory

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Abstract: The past hundred years have given birth to arguably the most profound changes in society, medicine, and technology the world has ever witnessed. Genetics is one such field that has enjoyed a meteoric rise during this time. Progressing from Mendelian genetics to the discovery of DNA to the ability to sequence the human genome, perhaps no other discipline holds more promise to affect future change than genetics. Technology currently exists to evaluate some of the genetic information held by developing embryos in the context of an in vitro fertilization (IVF) cycle. This information is then used to determine which embryos are selected for uterine transfer. Many societies have enacted legislation to protect against possible abuses utilizing this technology. However, it is incumbent upon society to continue ensuring that preimplantation genetic diagnosis (PGD)—and genetic testing in general—is applied in a way that utilizes its potential in a responsible manner to improve health care.

Keywords: DNA, genetic testing, PGS, PGD, embryo

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Since the dawn of civilization, mankind has placed great importance on our genetic composition. From the ancient civilizations of Egypt to the royalty of European nations today, the familial pedigree or bloodline of an individual has historically been of paramount importance in determining expectations and opportunity for advancement in society. In contrast, an ideal of many modern societies, often termed meritocracy, has been to move past the concept of inherited potential to allow individuals to achieve based on their merits alone.[1] Indeed, the capitalistic system that grew out of the United States tends to reward companies for hiring the best person for the job regardless of their background (but, of course, there are exceptions).

This environment has become a standard, that is, a new goal for western society. It is frowned upon for individuals to obtain a position in a company or school that is connected to a family donation. Politicians from humble backgrounds use their lack of connections in early life as a centerpiece of their campaigns. While individuals' family backgrounds certainly still shape their futures, this is far less of a factor today than arguably at any other time in human history.

Given this background of a growing social emphasis on allowing individuals to achieve and be judged on their merits, it is understandable that society is cautious about technology that could predict an individual's potential based on the results of genetic analysis. As genetic diagnostic technology continues to advance, our understanding of the genetic origins of disease is taking shape. We as a species are just now approaching the point where we can predict, to a limited degree, certain genes that may predispose an individual for a certain disease or condition.

This ability to diagnose genetic traits awoke basic fears of future abuse in the scientific community and society at large. An excellent example of these concerns is illustrated by the 1997 science fiction film *GATTACA*.[2] In the film, essentially all individuals in society are conceived in a laboratory at which time their DNA is sequenced and, based upon their genetic potential, their life (school, career, etc) are planned. In the GATTACA world, social class and potential are defined almost exclusively by an individual's genetic code, eerily similar to the blood line concept of inherited potential that has been a centerpiece of human history. The film chronicles the struggle of an individual with "nonideal" DNA to achieve greatness through tenacity and drive despite tremendous discrimination.

We are now able to identify single nucleotide polymorphisms (SNPs), markers on our genetic code, that if detected in a certain pattern are predictive, to some degree, of the development of such conditions as diabetes.[2–4] Several companies have begun to offer adult testing for predictive genetics. Predictive genetics technology tests for markers correlating with a slight increased chance of being diagnosed with a host of medical disorders ranging from depression to asthma.[5,6] Many of these tests are available without a physician's order and require only a saliva sample or a blood spot collection.[5–7]

This technology has been looked upon with concern by the medical and public policy communities. Specifically, the ability of the consumer to interpret the test results is questionable, especially in cases where the scientific foundation for the tested mutation, such as those associated with common conditions like depression, is lacking.[5–7] Such results could lead to potentially damaging and inaccurate information.[5–7] Additionally, while there are some regulatory mechanisms in place for such laboratories, some believe that more stringent regulations are warranted.[7,8] These concerns have led to consumer advocates and professional societies discouraging the public from using such testing services.[6,9,10]

For many disorders, such as Huntington's disease and cystic fibrosis, there are clear genetic mutations that are strongly tied to the development of disease. For the majority of medical disorders, such as type 2 diabetes and hypertension, however, what determines the development of disease appears to be more complex. At this point in time, an individual's family history and environment along with diet and exercise patterns are vastly more predictive of disease development compared to the currently defined associated disease markers.[2] It is believed that the disease markers currently described represent approximately 10% of total familial risk.[2] Therefore, as we continue to catalog more and more genetic markers associated with disease, our ability to predict disease based on genetics alone will exponentially grow. At some point, it is conceivable that genetic analysis will be the most predictive method by which

to assess risk for the development for many medical disorders.

Genetic testing is not limited to adults or even children. Preimplantation genetic diagnosis or PGD is a term used to describe the testing of human embryos in a laboratory for genetic disorders.[11,12] PGD is performed in conjunction with in vitro fertilization or IVF. IVF was developed as a modality for helping couples suffering from infertility. The procedure is accomplished by surgically retrieving eggs from human ovaries and fertilizing these with sperm in a laboratory. These fertilized eggs, or embryos, are then grown in the laboratory for 3 to 6 days and then placed in the mother's uterus.

More than 20 years ago, some laboratories began taking one or two cells from these developing embryos and conducting genetic tests on these cells.[13,14] In this way, limited amounts of genetic information could be obtained about the embryo, and this guided which embryos were placed into the uterus and which embryos were diagnosed with problems. As technology advanced, more detailed genetic analysis was possible, and specific genetic disorders that were known to exist in parents were able to be avoided in offspring through this process. PGD allows the selection of embryos with certain characteristics for uterine transfer and is, therefore, fundamentally different from purely diagnostic technologies such as fetal evaluation through maternal cell free DNA.

However, the early days of PGD were limited to testing for specific known parental genetic mutations and did not offer any insights into traits that could be perceived as otherwise advantageous such as intelligence, strength, and so on. Something that could be evaluated, however, was the sex of the embryo. There is increasing acceptance of the utilization of this technology in certain instances. For example, if there is a medical disorder in a couple's family that is sex-linked, that is, unmasked only in one gender, PGD for sex selection is generally accepted as an appropriate medical test.[12]

Sex selection PGD purely for a couple's gender preference is much more controversial. Several clinics have recently begun offering PGD purely so that parents may choose the sex of their child. Professional societies have formally opposed this practice on the basis that choosing an embryo purely based on gender is inherently sexist.[12,15,16] Others argue that PGD for gender selection is acceptable, especially for family balancing when a family may want to ensure that they are able to have a family with both male and female offspring.[16–19] There is a concern by some that, if adopted on a large scale, PGD for sex selection could lead to population imbalances in gender.[17–19] Consequently, PGD for sex selection is currently unlawful in many nations.[18,19]

Another controversial use of PGD has been for human leukocyte antigen (HLA) matching. This is generally used when a couple has an existing child with a condition, such as leukemia, that is in need of some human tissue transplant. In these cases, it is possible to run PGD to determine which embryos will be most similar to the sick child, through something called HLA matching.[12] The embryo with the closest HLA match is then transferred to the mother's uterus, and the resulting child will be destined to be a stem cell or organ donor.[12] This practice raises serious questions in regards to child exploitation.[18] This situation was the backdrop for the book *My Sister's Keeper* by Jodi Picoult in which a girl conceived through PGD for HLA matching becomes resentful of multiple donations for her sister who is suffering from leukemia. PGD for HLA matching also raises ethical issues in regard to the discarding of otherwise normal embryos that do not have an optimal HLA match. However, there are numerous examples of families that have successfully used PGD with HLA matching to treat an existing child with excellent results. An example of such a much publicized success story is the case of the Nash family in which umbilical cord blood from an HLA-matched sibling translated into a significant benefit for an existing sibling with Fanconi anemia.[20]

Perhaps the most contentious use of PGD currently is the concept of looking for traits that one would desire in embryos. The technology to achieve this is now available. In 2007, scientists in Europe identified single nucleotide polymorphism (SNPs) that are associated with a host of physical traits such as eye color, hair color, and freckles.[21] Though clinics are not currently offering PGD for these traits, from a technologic point of view, this is almost certainly a possibility in the future.

We are at the dawn of the age of genetics. The awesome power of the technology that is emerging is difficult to fully appreciate at this point in time.

As described in the film *GATTACA,* the ability to define an individual by a genetic code has at its core the potential for widespread and terrible abuse. A slippery slope exists with this technology of which we must always keep mindful. The ability to assess risk of developing medical conditions based on genetics has the potential to introduce widespread discrimination throughout society. One could envision a future where employers or insurers base decisions in part on one's risk of illness according to a genetic readout. In anticipation of such discrimination, The Genetic Information Nondiscrimination Act of 2008 was enacted in the United States with the expressed purpose of preventing such genetic-based discrimination in the arenas of health insurance and employment.[22]

Still more disturbing is a world, as in GATTACA, in which parents choose embryos with PGD that possess genetic traits optimal for success. We currently have the technology to choose embryos based on sex. Surely in the near future, we will be able to identify genes and DNA sequences that code for a host of other traits such as height, intelligence, strength, and so on. The inequities that could arise from this sort of PGD have no parallel in human history. As PGD is only available in wealthy nations and, in general, to wealthy individuals within these nations, the construct exists for people with means to weight the genetic scales in their favor. As GATTACA illustrated, this technology has the potential to ultimately redefine society in an extremely negative way. This outcome is unacceptable. In many nations, regulations have been created to preempt some of the potential negative social consequences that may result from PGD.[12] However, it is incumbent upon society to continue ensuring that PGD—and genetic testing in general—is applied in a way that utilizes its potential in a responsible manner to improve health care. This can only be accomplished through a constant and thoughtful social dialogue.

Author Contributions

Conceived and designed the experiments: PRB. Analyzed the data: PRB. Wrote the first draft of the manuscript: PRB. Contributed to the writing of the manuscript: PRB. Agree with manuscript results and conclusions: PRB. Jointly developed the structure and arguments for the paper: PRB. Made critical revisions and approved final version: PRB. All authors reviewed and approved of the final manuscript.

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