PREIMPLANTATION GENETIC TESTING

Preimplantation genetic testing for polygenic disease risk

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Abstract

Since its introduction to clinical practice, preimplantation genetic testing (PGT) has become a standard of care for couples at risk of having children with monogenic disease and for chromosomal aneuploidy to improve outcomes for patients with infertility. The primary objective of PGT is to reduce the risk of miscarriage and genetic disease and to improve the success of infertility treatment with the delivery of a healthy child. Until recently, the application of PGT to more common but complex polygenic disease was not possible, as the genetic contribution to polygenic disease has been difficult to determine, and the concept of embryo selection across multiple genetic loci has been difficult to comprehend. Several achievements, including the ability to obtain accurate, genome-wide genotypes of the human embryo and the development of population-level biobanks, have now made PGT for polygenic disease risk applicable in clinical practice. With the rapid advances in embryonic polygenic risk scoring, diverse considerations beyond technical capability have been introduced.

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Introduction

Many advances have been made since the first reported clinical use of PGT for a monogenic disease (PGT-M) (Handyside *et al.* 1990). For example, PGT has expanded to include routine evaluation of chromosomal aneuploidy (PGT-A) and structural rearrangements (PGT-SR). Utilization has now reached approximately one-third of all *in vitro* fertilization (IVF) cycles in the United States (Society for Assisted Reproductive Technology 2018; <https://www.sart.org>). PGT methods have also evolved, with the development of new, cost-effective and high-throughput human genome sequence analysis tools. As described in this review, machine learning applied to data from population-level biobanks now provides the opportunity to expand PGT to more common, genetic diseases which are polygenic in nature.

Population level polygenic disease risk

According to the World Health Organization (WHO), approximately 26% of the world population will die prematurely from a non-communicable disease (NCD), and total disease incidence is higher still. The WHO estimates that 80% of NCDs can be attributed to cardiovascular disease, respiratory disease, cancer,

and diabetes (i.e. polygenic disorders) (World Health Organization 2014). Relative to the percentage of the population affected by a monogenic disease, the world-wide indication for polygenic disease risk may be more than ten times greater.

Significant national and commercial efforts have been made to establish large biobanks to help researchers improve population health (Table 1). Among these repositories is the United Kingdom BioBank (UKBB), which includes genome-wide DNA data from 500,000 individuals (Sudlow *et al.* 2015). The UKBB ‘aims to improve the prevention, diagnosis and treatment of a wide range of serious and life-threatening illnesses – including cancer, heart diseases, stroke, diabetes, arthritis, osteoporosis, eye disorders, depression and forms of dementia’. Although this repository is enriched for healthy individuals, the prevalence of disease (Table 2) has made it possible to develop useful polygenic risk scores for many common diseases, including those among the top ten causes of death.

Polygenic risk scoring (PRS)

Genome-wide association studies (GWAS) were initially applied with the idea that small numbers of genetic loci would be adequate to explain variation in complex

Table 1 Examples of population level biobanks suitable for development of polygenic disease risk predictors.

Biobank name	Number of individuals*
United Kingdom Biobank	500,000
Biobank Graz	1,200,000
'All of Us' Biobank	1,000,000
The International Agency for Research on Cancer (IARC) Biobank (IBB)	562,000
China Kadoorie Biobank	510,000
FINNGEN Biobank	500,000
Canadian Partnership for Tomorrow Project Biobank	300,000
Qatar Biobank	60,000
Biobank Japan	200,000
Million Veteran Program	1,000,000
Genome Asia 100K	100,000

*Number of individuals set as recruitment goal.

disease phenotypes in a population (Klein *et al.* 2005, Dewan *et al.* 2006). Advances in bioinformatics have led the GWAS methodology, reporting individually associated loci, to be superseded by genomic prediction methodology, with a focus on prediction competence through polygenic risk scoring (PRS). A result has been the rapid growth in research and development of PRS (Fig. 1). The PRS approach can be considered an evolution of the GWAS. While a GWAS measures a single locus' correlation with a given disease, and typically defines success as a high degree of association of a given locus, a PRS approach measures capability to distinguish different phenotypes, such as disease and non-disease, using combinations of loci, and defines success as capability to accurately predict the phenotype of interest.

The combination of PRS and standard clinical risk indicators (Chatterjee *et al.* 2016, Torkamani *et al.* 2018) has now made it possible to identify individuals with elevated polygenic disease risks equivalent to the elevated risk of individuals with monogenic diseases, including breast cancer, type 2 diabetes, and atrial fibrillation (Khera *et al.* 2018). Several studies have also demonstrated the ability of PRS to explain polygenic disease phenotypes directly from an individual's DNA (without clinical indicators). For example, Lello and colleagues recently reported on PRS performance for diseases including hypothyroidism, hypertension, type 1 and 2 diabetes, breast cancer, prostate cancer, testicular cancer, gallstones, glaucoma, gout, atrial fibrillation, high cholesterol, asthma, basal cell carcinoma, malignant melanoma, and heart attack (Lello *et al.* 2019).

Table 2 WHO estimates and UKBB values for common polygenic disease prevalence.

Disease	World	UKBB
Cardiovascular	31%	3%
Cancer	17%	9%
Diabetes	9%	5%

Infertile population polygenic disease risk

The WHO estimates that 10% of women are affected by infertility, with *in vitro* fertilization (IVF) considered the most effective treatment. Reviewed by Cedars *et al.* (2017), and now supported by the NIH, it is well established that infertile individuals are less healthy than fertile individuals, with increased risk for cardiovascular disease, cancer, and diabetes. Increased prevalence translates to better performance (higher utility) of clinical tests. Therefore, better performance of PRS in embryos derived from infertile couples can be expected, compared to the population without this indication. Determining whether IVF-derived embryos have an increased prevalence of high polygenic risk scores relative to the general population is in fact the objective of ongoing research. Initial data suggest that polygenic disease risk reduction performance with genetic testing in the UKBB and T1DBase (Burren *et al.* 2011) is significant (Treff *et al.* 2019a,b).

PGT for polygenic disease risk (PGT-P)

Four years following the first reported birth following PGT for a monogenic disease (Handyside *et al.* 1992), Nobel Laureate Robert Edwards and his colleague Joseph Schulman proposed that 'many of the major human traits are highly polygenic, and that a large number of genes may possibly be analysed in embryos in the near future' (Schulman & Edwards 1996). However, only recently has this become a reality, as the first reported clinical application of PGT for polygenic disease risk (PGT-P) was published in 2019 (Treff *et al.* 2019a), which includes analysis of multiple diseases (Fig. 2). This capability required several major developments: first, the availability of population-level genome-wide data with corresponding clinical phenotypes; second, the ability to perform accurate genomic prediction of a complex

Figure 1 Thirty years of publication since the first PGT. PGD-preimplantation genetic diagnosis, PRS-polygenic risk scoring. (A) The first PGT cases reported (Handyside *et al.* 1990); (B) the first PGT birth reported (Handyside *et al.* 1992); (C) the first human whole genome sequence (WGS) published (Lander *et al.* 2001); (D) the first genome-wide association study (GWAS) reported (Klein *et al.* 2005); and (E) the first PGT for polygenic disease risk (PGT-P) reported (Treff *et al.* 2019a).

Figure 2 Example PGT-P report for a female embryo.

human trait (Lello *et al.* 2018); third, the capability to obtain embryonic genome-wide genotypes with accuracy equivalent to adults (Treff *et al.* 2019b); and fourth, the capability to achieve significant reduction in polygenic disease risk following genetic selection of a sibling (Treff *et al.* 2019a).

The latter of these developments, demonstrating clinical utility in genetic selection across >2000 siblings, is an important outcome to highlight. First it requires that one appreciate that genotypes obtained in embryos are equivalent in accuracy to genotypes obtained in adults. With that in mind, one can evaluate adult sibling cohorts with known disease status to determine the utility PGT-P in sibling embryo selection. When compared to random selection, the use of genetic selection demonstrated 45–72% reduction in the prevalence of type 1 diabetes. This demonstrates that choice is significantly better than chance when considering a sibling embryo's risk of polygenic disease.

Many additional considerations regarding the application of PGT-P are currently under investigation. For example, the quiet embryo hypothesis (Leese 2002) suggests that selecting more metabolically active embryos could increase the risk of adult-onset disease (including diabetes, cancer, and cardiovascular disease). Embryo selection based on morphology (Gardner *et al.* 2015) may contribute to this phenomena. As utilization of IVF and PGT-P increases, the correlation between embryo morphology and polygenic disease risk will be evaluated.

The concept that selection against one disease may increase the prevalence of another (pleiotropy) (Zheutlin *et al.* 2019) may be addressed using a 'genomic index' selection methodology, which provides combined risk scoring across multiple disease risks,

much as PRS provides combined scoring across multiple genomic regions. Indeed, recent data suggest that the genetic loci used to predict different diseases are largely disjoint (Yong *et al.* 2020), such that selecting against one disease will not increase the risk of another. In fact, the impact of pleiotropy may be in the positive direction, where for example, selection against high risk of hypercholesterolemia might also result in reduced risk of myocardial infarction. This is one focus of ongoing research.

PGT-P ethics

Health care disparity may result from the limited representation of ethnicities made available by existing biobanks. Polygenic predictors constructed using a preponderance of a single ethnic group (typically, European ancestry) perform well when predictions are made within the same ethnic group, but less well when predictions are made outside the ancestral training set. Prediction accuracy decline follows the overall genetic distance between the training ancestry and target ancestry. This leads to a situation where, for example, predictions may be more beneficial for Europeans and less so for Africans and Native Americans. As Table 1 indicates, efforts throughout the world can be expected to eliminate this disparity when applying PGT-P in the near future.

The cost of IVF and PGT-P may also limit its use to individuals with the economic means to access care, causing increased disparity in health between wealthy and poor in the next generations. Several IVF programs have begun developing 'low-cost' IVF options, while others have developed methods which allow PGT without IVF (Munné *et al.* 2020). These efforts, in combination with national and commercial insurance policy changes, may help eliminate the potential for economic disparity in application of PGT-P.

A third ethical consideration involves appropriately defining what phenotypes should be tested. Mainstream media has focused on the possibility of using PGT-P to test for desirable traits, often referred to as selection for 'designer babies'. A recent report evaluating selection for increased height and cognitive ability suggests that this application may not (yet) be powerful (Karavani *et al.* 2019). Still, some argue that selecting against embryos with high risk of disease is itself a designer baby outcome. However, an American Society for Reproductive Medicine Ethics Committee argues that testing embryos for adult onset conditions of lesser severity or lower penetrance is ethically justifiable for reasons of reproductive liberty (ASRM-Ethics-Committee 2018). It has been argued, in both PGT-M and PGT-P, that there is no need to select against diseases of lesser severity, on the grounds that they are treatable. However, even treatable diseases, like type 2 diabetes, impact lifespan.

The disease panel for which PGT-P screening is possible is largely determined by the availability of data for machine learning (Table 2). As the data grow, and as government, social, and health care policies are adapted, definitions of what is appropriate to test may evolve. These efforts have already begun with the European Commission's recent Joint Research Centre report on 'genome-wide association studies, polygenic scores and social science genetics: overview and policy implications'. The report suggests that the availability of PGT-P 'illustrates how fast GWAS may influence the sector and demands the policy makers' and society's response on how to determine the margins and deal with these possibilities'. (European Commission 2019).

Gene editing

In 1996, Edwards and Schulman also raised the possibility of reducing the symptoms of inherited disease through 'germinal DNA therapy' (Schulman & Edwards 1996). The introduction of gene-editing (i.e. CRISPR/Cas9) in the preimplantation embryo has stirred considerable debate, and possible scientific misconduct (Cyranski 2019), but also exciting new research on the opportunity to cure disease before pregnancy (Lea & Niakan 2019). Interestingly, this opportunity may lead to increased acceptance of PGT, where the outcome may no longer involve discarding embryos, but instead correction for the genetic abnormality with subsequent utilization for embryo transfer. New research involving the creation of gene-edited-embryo-derived embryonic stem cells (Ma et al. 2017) may be instrumental in the development of rigorous safety and efficacy data, but also to aid in development of the necessary genome-wide PGT methodologies. Applications beyond curing monogenic diseases may include curing Down Syndrome in embryos derived from Robertsonian translocation carriers (t21:21), restoring euploidy via polar body and parental DNA genetic analyses, and curing polygenic diseases through the identification and editing of multiple causative genetic loci. The prospect of targeted edits for the treatment of polygenic diseases remains unproven as the identification of the true causal set of loci is difficult to disentangle from loci which may only be correlated with the causal variants (i.e. those loci used for PGT-P). Much research remains in the effort to resolve the true genetic architecture for polygenic disorders, but the prospect of such a public health benefit remains tantalizing. In all cases, genome-wide PGT will remain a necessity, as will maturation of public policy (Ormond et al. 2017), if gene-editing is to make it to its intended clinical use.

Conclusion

Infertility is a growing public health concern, as is the global rate of premature death from polygenic disease. Initial application of PGT-P may be well suited to

the infertile population given their increased risk of cardiovascular disease, cancer, and diabetes and the current clinical practice of selecting more metabolically active (not quiet) embryos for transfer. By combining the power of machine learning, large biobanks, and state-of-the-art molecular genetics, the introduction of PGT-P to clinical use may provide a means to reduce the prevalence of disease in humans. Evolving public policy around reproductive liberty and increased access to care, expansion of more diverse DNA repositories, and additional research on the relative disease risk reduction to offspring from parents with distinct indications, will be instrumental in realizing the full untapped potential of preimplantation genetic testing for polygenic disease risk.

Declaration of interest

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