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The alarming rise of complex genetic testing in human embryo selection

Companies are marketing polygenic risk scores as part of IVF well before the potential benefits — and dangers — are fully understood.

The emergence of companies that offer prospective parents complex genetic tests on embryos ahead of *in vitro* fertilization (IVF) has alarmed geneticists and bioethicists alike. The companies claim to be able to predict the risk of many common diseases — including those influenced by dozens or even hundreds of genes. People undergoing IVF are then offered the chance to select an embryo with a perceived low relative risk of developing such diseases.

Researchers are right to be concerned. The selection of embryos on the basis of these predictions is not yet supported by science. Moreover, the societal implications of using complex genetic tests to choose embryos has not yet been fully considered. Some scientists are completely opposed to the practice, whereas others recognize that, as more data accrue, there might be benefits, but realize that it must be carefully regulated. A study published in *Nature Medicine* on 21 March explains some of the methodology behind the determination of what are called polygenic risk scores and draws attention to the practice — but does not allay scientists' fears (A. Kumar *et al. Nature Med.* **28**, 513–516; 2022).

Some health authorities around the world do regulate the use of simple genetic testing alongside IVF, but many do not. The aim of these tests is to reduce the chances of a parent transmitting an inherited disease to their unborn child — typically in the case of rare, devastating conditions caused by mutations in a single gene. In the United Kingdom, for example, tests have been approved by the Human Fertilisation and Embryology Authority for more than 600 inherited disorders, including Tay–Sachs disease and breast cancers caused by mutations in the genes *BRCA1* and *BRCA2*.

But the most common diseases, such as type 2 diabetes, are associated with mutations not in a single gene, but in many — potentially even thousands. To understand genetic contributions to such conditions, researchers have been analysing DNA sequences from many thousands of people with the disease, and comparing them with the DNA of people who do not have it, looking for genetic variants that are associated with a higher risk of developing the condition. This information is then converted into an overall score that estimates a person's relative risk of developing the disorder. But there's a consensus that the scores are not yet ready to be used beyond research studies.

> **"These tests demand a broader societal discussion."**

In the *Nature Medicine* study, the authors — most of whom work for companies involved in IVF or genetic testing — address the technical challenge of predicting accurate genome sequences from the small amounts of DNA available from one or two cells biopsied from an embryo. The researchers constructed sequences for more than 100 embryos by analysing hundreds of thousands of sites in the embryos' genomes using a technique called genotyping, which requires less DNA than whole-genome sequencing does. They then combined these data with whole-genome sequences from the parents to fill in the rest of the DNA sequences and, in ten cases, compared the reconstructed genome from an embryo with the full genome sequence of the resulting born child. They found that they were able to infer the correct genome sequence at sites used to calculate polygenic risk scores for 12 conditions — including diabetes, certain types of heart disease and several forms of cancer and autoimmune disorder — with 97–99% accuracy.

The authors say that the technique described in the study, which has been peer reviewed, establishes the feasibility of assessing genomic regions necessary to calculate a polygenic risk score for an embryo. But this technical capability is not the main reason for concern and debate over the use of polygenic risk scores in embryo selection for IVF.

There are other, bigger, concerns. One is that the scores have been developed on the basis of genome-wide association studies that have disproportionately sampled DNA from people of European descent. Although efforts are under way to diversify such databases, the scores currently available are not based on an appropriately diverse subset of people. Even among white European people, polygenic risk scores are sometimes predictive only in narrow subsets of that population — potentially, in part, because of poorly understood interactions between the genetic and environmental contributions to a condition.

Furthermore, scientists do not yet fully understand how the selection of embryos with a lower relative risk for one disease might influence susceptibility to other conditions. Genetic variation can have a number of effects — a phenomenon known as pleiotropy — and a DNA sequence associated with one beneficial characteristic could also increase the risk of a detrimental one.

Many of these polygenic scores are being used to predict the risk of disorders that occur later in life, without any way of incorporating changes in environment that could occur over that time. A child born today will probably not experience heart disease or diabetes for decades, and there is no way of knowing what treatments or preventive steps will be available by then, or what changes in the environment might have taken place.

Concerns about under-represented populations and pleiotropy might be addressed with further research. But polygenic risk assessments are already being marketed directly to consumers (and not only for IVF) in some countries, including the United States and Japan. It is not clear to what extent individuals are counselled on the technique's uncertainties and risks. Meanwhile, the scores of

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such assessments could be harmful. They could trigger the unnecessary destruction of viable embryos or induce women to undergo extra cycles of ovarian stimulation to collect more oocytes.

For now, prospective parents seeking IVF should not be offered polygenic risk scores for diseases unless they are part of rigorous clinical trials. Professional societies should make this clear to their members — as some have already done — and should publish guidelines on how to counsel participants in such trials to avoid giving them false hopes or fears about their children's health. Genetic counsellors must be trained to do the same.

These tests demand a broader societal discussion. By nature of their complexity, polygenic risk scores open the door to evaluating not only disease risk, but also traits such as height or intelligence. At present, not enough is known about the genetic contributors to such traits to develop meaningful tests that would allow prospective parents to select embryos. But those data are on the way and the technology is going to move quickly — it is well past time to discuss how far it should go.

This is no time to stop tracking COVID-19

To live with the coronavirus, we cannot be blind to its movements.

From the way political leaders in many high-income nations are talking and acting, it would be easy to think that the COVID-19 pandemic is no longer worth keeping track of.

The pandemic might have taken upwards of 18 million lives, disabled many more than that and gut-punched the global economy, yet surveillance and reporting of the virus's movements are starting to slow just at a time when a highly infectious subvariant of Omicron, BA.2, is spilling out across the world and case rates and hospitalizations are creeping back up.

These cutbacks are not based on evidence. They are political, and they could have disastrous consequences for the world. Maria Van Kerkhove, technical lead for COVID-19 at the World Health Organization (WHO), says it's crucial that "the systems that have been put in place for surveillance, for testing, for sequencing right now be reinforced, that they are not taken apart".

Around the world, the frequency of national reporting has slipped below five days a week for the first time since the early months of the pandemic, according to the publishers of the website Our World in Data. In the United States, the Centers for Disease Control and Prevention (CDC) is still reporting nationwide data, but there's less real-time reporting of death and infection figures at the local level. All but eight states have scaled back to reporting data five or fewer days per week. Florida announced last week that it will now be reporting only fortnightly.

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The UK government's COVID-19 tracking dashboard, one of the world's most comprehensive, is stopping its weekend updates of infections, mortality, hospitalizations and vaccinations, lumping Saturday and Sunday figures into Monday's. Prime Minister Boris Johnson says this is part of plans to "live with COVID".

The downward trend in reporting is subtle, but it mirrors other signs of complacency about COVID-19. The United Kingdom, for example, will no longer provide diagnostic tests free of cost. Several of its data-collection programmes are also ending. REACT-1, a long-running random-testing study, will lose its government funding at the end of this month. And ZOE, a mobile app that residents can use to log their COVID-19 symptoms, has lost its public funding, too. Both have been invaluable to research and policy.

The United States and United Kingdom aren't alone. In many countries, political sentiments are shifting towards adopting a 'new normal'. Of course, national budgets are being stretched thin as governments look to increase public expenditure on subsidizing fuel and food as the world plunges from dealing with the pandemic to tackling the global impacts of war in Ukraine. But scaling back virus surveillance at this time is short-sighted. It's like stopping a course of antibiotics at the first sign of symptoms easing: it increases the risk that the infection will roar back. A study published last week says the next variant could well be more dangerous than those circulating now (P. V. Markov *et al*. *Nature Rev. Microbiol.* https://doi.org/hk3q;2022).

Public-health decisions need to be informed by the best available data. Cutting the ability to track and respond to the virus while most of the world remains unvaccinated makes these decisions less reliable. It will also reduce people's ability make decisions about their own safety.

This is all the more infuriating given that roll-backs of public-health interventions have often come with messages that people should now decide for themselves what measures to take. The CDC, for example, recommends that people at risk of serious complications from COVID-19 "talk to their healthcare provider" about whether they should wear a mask or respirator during "medium" community transmission levels — just when data on transmission are becoming less accessible.

Researchers have worked hard (see page 564) to make disparate sources of data about the pandemic available to the public through several celebrated dashboards. Tools such as the WHO Coronavirus (COVID-19) Dashboard, Our World in Data and Johns Hopkins University's COVID-19 Dashboard have empowered governments, businesses and individuals to use the best available evidence to make decisions. By reducing the data streams that power these dashboards, governments are shutting their eyes to the danger. If this trend continues, the new normal is going to look a lot like the false comfort of ignorance.

Correction

The Editorial 'The alarming rise of complex genetic testing in human embryo selection' incorrectly stated that whole-genome sequences were taken from "prospective parents" of embryos, when in fact they were taken from actual parents. In addition, the ten children whose genomes were used for comparison with the reconstructed genomes were the resulting born children, not siblings.

Corrected 28 March 2022