Polygenic risk predictions:
health revolution or going round in circles?

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A report by GeneWatch UK

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1. Introduction

Polygenic Risk Scores (PRSs) are a new way of calculating people's genetic risks of common diseases, such as heart disease, cancers and diabetes. PRSs are based on statistical calculations made by computer algorithms from millions of small differences in people's DNA, each of which is associated with only a tiny (sometimes negligible) difference in risk. The idea is that these calculations will identify people who are at 'high genetic risk' of common diseases, so that these people can be treated before they become ill: for example, by taking medicines to reduce the risk of disease.

There are significant commercial interests driving the idea that everyone should have their genetic information stored for life. Some companies (mainly in the USA) are already selling PRSs online, and there are plans to use them in health services. In the UK, there are plans to provide PRSs to people taking part in a major new project called 'Our Future Health'. Volunteers will be recruited via the National Health Service (NHS) but the storage and analysis of data will be undertaken by commercial companies. In the USA, the eMERGE (electronic MEdical Records and GEnomics) network also plans to return PRSs to participants. Studies in other countries are also investigating this approach, but most have yet to take final decisions on whether PRSs will be fed back to individuals.

This report asks whether PRSs will be good for health and considers their implications for society.

Currently, most people do not have genetic testing, unless it is directly useful to their health, and, even then, usually only small parts of a person's DNA are tested. In contrast, calculating PRSs requires large databases of people's personal information and their DNA, which raise significant concerns about privacy, surveillance and the potential for discrimination. Every individual and their relatives can be tracked through their DNA, which acts like a 'genetic fingerprint' and can reveal personal information, such as non-paternity in families. Plans to feedback PRSs to individuals will inevitably lead to access to such information by governments, police and private companies. This report asks, is this level of intrusion, and the associated costs, justified by the claimed benefits to health?

2. Genetic disorders, common disorders, and the role of PRSs

Genetic disorders, such as cystic fibrosis and sickle cell disease, which are caused by specific mutations (small changes) in a person's DNA, are relatively rare and often cause symptoms in childhood. Having a genetic test can help to diagnose such illnesses, usually in people (often babies) who are already sick. However, most diseases, including the 'big killers', such as cancers and heart disease, are much more complex and involve numerous environmental and biological factors, as well as chance.

Many of these complex conditions can be divided into rare 'familial' and common 'sporadic' forms. For example, rare mutations in the BRCA1 and BRCA2 genes can cause largely inherited forms of breast or ovarian cancer. These mutations do not mean a person necessarily develops breast or ovarian cancer, but they do mean that they are at much higher risk, to the extent that some women choose to have surgery to remove their breasts and/or ovaries before cancer develops. However, familial breast cancer accounts for only about 1.8 to 2.6% of all breast cancer cases and these mutations are only detected in 25% of families with a strong history of breast cancer.[1,2] Not everyone with mutations in these

genes will develop cancer (one study estimates that about 38% of women with these mutations do[3]), although the risk conferred by having these mutations is higher in women from families with multiple breast cancer cases (up to an 87% of developing breast cancer by the age of 70).[4,5] There are difficulties in interpreting the risk conferred by having (or not having) genetic mutations in the general population, because a given mutation generally carries a lower risk in the general population than in high-risk families with known cases of disease, and the significance of some mutations is unknown.[6] Thus, this type of genetic test is normally only offered to high-risk families (based on family history) in health services, rather than being used as screening tests for whole populations. There are many other examples of 'familial' diseases, such as familial hypercholesterolaemia (an inherited form of high cholesterol levels), where relatively rare mutations in particular genes confer a high risk, but do not explain high cholesterol levels in most people. For Alzheimer's Disease, there is an early onset form in which about 5% of cases carry a rare mutation in one of three known genes.[7] Whilst some researchers advocate screening the whole population for some of these mutations in the future, in order to identify the 1% to 2% of the population expected to be identified as at risk, there are many barriers to doing so in practice.[8] These 'familial' conditions (also known as 'monogenic', since they often involve a mutation in a single gene) are not discussed further in this report, as identifying them requires different technology and methods from those used in polygenic risk scores (PRSs). In particular, the DNA chips used to measure the genetic differences called SNPs which are used in PRSs, do not identify these rare mutations well.[9] Nevertheless, some research projects (such as the eMERGE network in the USA, discussed in Section 9) may combine PRSs with additional tests for some of these rare mutations.

Much research that takes place today has moved beyond these 'familial' conditions and involves studying to role of genes in the more common so-called 'sporadic' (non-familial) forms of cancer or other common diseases, known as 'complex' diseases. For these diseases there are some common genetic variants which can increase a person's risk. One of the strongest effects is the effect of the APOE gene on Alzheimer's Disease (first discovered in 1993). There are three different common versions of this genetic variant (as well as some rare ones), and the variants which lead to a lower level of the associated protein apolipoprotein E (apoE) in a person's blood increase their risk of Alzheimer's.[10] Each person has two copies (known as alleles) at a given location in their genome, so people with two copies of the highest risk genetic variant (known as the e4/e4 genotype) are at the highest risk (estimated as a 30% to 55% lifetime risk of developing Alzheimer's).[11] Testing the APOE gene is not recommended because it does not provide sufficient sensitivity or specificity to allow genotyping to be used as a diagnostic test – meaning that many people with the high-risk variants do not develop Alzheimer's and many without the high risk variants still develop the disease.[12] Other common variants exist which alter the risk of other common diseases, however, the effect of the APOE gene on the risk of Alzheimer's Disease is much greater than generally observed for common genetic variants in common diseases, and most common variants have tiny effects.[13,14] Alongside evidence that many common diseases have an inherited component (see Sections 6 and 7), this led many researchers to believe that most of the effect of genes on the risk of common diseases is hidden in the combined effect of many rarer genetic variants.

Polygenic Risk Scores (PRSs) are developed using the results of research known as Genome Wide Association Studies (GWAS). These studies seek to identify variations in people's genomes that are statistically associated with a risk for a disease or a particular trait (such as a person's height or eye colour). They use large databases, such as UK Biobank, which contains data from half a million people, including their DNA and information about the diseases they develop (taken from medical records). The genetic differences (called 'polymorphisms') that are studied are called Single Nucleotide Polymorphisms (SNPs, pronounced 'snips'). To be classified as a SNP, a genetic variant must be found in at least 1% of the population. Some more recent studies instead refer to single nucleotide

variants (SNVs), which can include genetic variants that are rarer than SNPs. SNPs and SNVs are places in a person's DNA (their 'genome') which differ from other people's DNA by a single chemical letter (known as a 'nucleotide'). Polymorphisms are more common than rare genetic mutations which sometimes cause genetic disorders. They are genetic variations which are thought to usually increase or decrease a person's risk of disease very slightly, perhaps by changing the expression of a gene (how much of a particular protein is produced) rather than stopping the gene from functioning. The SNPs that are identified using GWAS as being statistically associated with an increased risk of disease don't generally play a causal role in a disease: they are thought to tag genetic variations that do play a causal role and which have been inherited together with the identified 'tag SNP' (see Section 7). To create a PRS, small effects on risk in multiple rare genetic variants are combined using computer algorithms. The tiny effects on risk associated with millions of SNPs may now be included in a single PRS. It is important to be aware that different companies and different research groups may use different algorithms and get different results (see also Section 5).[15]

In general, PRSs seek to calculate the genetic risks of 'big killer' diseases in Western countries. Examples of such common, chronic diseases include heart disease, diabetes, Alzheimer's, psychiatric diseases, cancers and autoimmune disorders such as rheumatoid arthritis and multiple sclerosis. The risk of developing these diseases depends on multiple factors, such as a person's environment, lifestyle and biology, including their DNA, plus an element of chance.

PRSs that are on the market today, or that are being considered for use in health services, measure parts of a person's genome using DNA chips (also called SNP chips or microarrays). These use probes to identify particular chemical letters (C, G, A or T) that make up the so called 'genetic code' at particular places in the genome. Newer technology, called Whole Genome Sequencing (WGS) measures all the chemical letters (all of a person's DNA, or their whole genome), but is still too expensive for widespread use. DNA chips typically include millions of SNPs and data from these SNPs are combined into risk scores using computer algorithms. Many of the algorithms used to calculate PRS also use what is known about the human genome from existing WGS studies to estimate some of the chemical letters that are not measured directly (this is known as 'imputation'). Earlier versions of the algorithms used tens or hundreds of SNPs and were often known as Genetic Risk Scores (GRSs), rather than Polygenic Risk Scores (PRSs), although the terms PRS and GRS are used in different ways by different people. The term Polygenic Score (PGS) is also sometimes used. Although there is no clear distinction between the definition of a GRS and a PRS, the former usually require fairly strong evidence that a SNP plays a role in a disease, whereas the latter typically include millions of SNPs which have close to zero effect on the risk of the disease, and which do not meet the traditional idea of what is a statistically significant effect (the usual way of trying distinguish between an effect that is real or is just due to chance).[16] Questions about the reliability of PRSs are an important part of this report.

The individuals and companies promoting PRSs believe that one day everybody should take these tests, meaning that everybody's DNA would be stored in vast connected databases. This is a big step beyond the kinds of genetic testing that are used today, as many more people would be tested (the aim is to test whole populations, most of whom are healthy, to predict disease, rather than to diagnose relatively rare diseases in much smaller numbers of people) and much more data would be stored (sufficient to identify every individual and their relatives via their 'genetic fingerprint').

3. Genetic 'prediction and prevention' of disease: a history of misleading claims

"…*we can now see a future where the doctor will swab a few cells from inside your cheek, put them into a DNA-sequencing machine and a computer will spit out a complete reading of your unique genetic makeup - all 30,000 or so genes that make you who you are. From that, doctors could pinpoint flawed genes and gene products and predict what diseases you are likely to develop years in advance of any symptoms - and how to help you avoid them*."[17] UK Prime Minister Tony Blair, 2002.

The idea that calculating genetic risks for everyone could be good for health dates back to the Human Genome Project (HGP), which ran from 1990 to 2003. Linked with the need to obtain funding for this and subsequent projects, leading scientists made many unsubstantiated promises to politicians about the 'prediction and prevention' of common diseases.[18] False claims by tobacco industry-funded scientists that genetic screening would identify the one in ten smokers likely to develop lung cancer, supposedly allowing the remainder of the population to smoke with impunity, were endorsed by leading scientists in the run up to the HGP, as they battled to convince the Thatcher and Reagan governments that the research would have industrial applicability.[19] In the US, a leading advocate of this approach was Dr Francis Collins (then the Director of the Human Genome Project in the USA, subsequently the Director of the National Institutes of Health, and Science Advisor to the US President).[20] In the UK, Oxford University's Professor Sir John Bell, who now holds an influential position as the UK Government's 'Life Sciences Champion', has been an enthusiast for identifying genetic susceptibility to common diseases since the 1990s.[21] The idea of genetic 'prediction and prevention' of common diseases led to several controversial failed attempts by the UK Government to allow medical data collected from individuals to be shared without their knowledge or consent, and, in 2003, the Blair Government proposed sequencing the DNA of every baby at birth, arguing that the babies' genetic information "*could then be used throughout their lifetime to tailor prevention and treatment regimes to their needs as further knowledge becomes available about how our genes affect our risk of disease and our response to medicines*".[22,23]

Many scientists argued at the time that the claims made about the medical value of tests for 'genetic susceptibility' to common diseases had been over-sold by the enthusiasts for this approach.[24,25,26,27,28,29,30,31,32,33,34,35] A major concern was that the idea of 'personalised prediction' undermines the idea of public health, where efforts to improve environments, lifestyles and socio-economic circumstances should not depend on people's genes.[36] Despite much misleading hype, by 2008, none of the 'genetic susceptibility' tests that had been developed were of sufficient predictive value to be used, although many misleading tests were sold by private companies.[37]

These older tests tried to combine the risk of a relatively small number (at most tens) of genetic variants. New technologies (DNA chips and whole genome sequencing) and faster computers mean that it is now possible to attempt to calculate a person's genetic risk of common diseases using complicated computer algorithms which combine the effect of hundreds, thousands, or even millions of genetic differences, known as SNPs, to create a Polygenic Risk Score (PRS). However, many scientists and medical professionals remain sceptical about the value and reliability of these risk predictions and their usefulness for health.[38] The reasons for this scepticism are explored further below.

In the discussion below, we first assume that the new calculations of genetic risk included in Polygenic Risk Scores (PRSs) are correct, and ask whether these predictions would be good for health. Then we consider potential problems with the computer algorithms used to calculate the scores, and ask whether they can be trusted by the individuals taking them.

4. Can lifestyle advice tailored to genetic test results improve population health?

"*The development and use of polygenic scores is attracting money and attention, but, for most common diseases, unglamorous but well established risk factors like smoking, obesity, and socioeconomic deprivation matter more than a person's genetic background. Childhood postcode, for example, is probably as good a predictor of risk for most common diseases as most polygenic scores*". Medical researchers writing in the British Medical Journal, 2023.[39]

Polygenic Risk Scores (PRSs) aim to identify a small proportion of the population (for example, the top 5%, or 10%) who are at highest genetic risk of a disease. In a highly individualised approach, instead of taking steps to improve the health of the whole population, only people at 'high genetic risk' are encouraged to take steps to improve their lifestyles. For example, the CEO of the US gene testing company 23andMe, Anne Wojcicki, has stated, "*When customers learn about their genetic likelihood of developing Type 2 diabetes, we believe there is an opportunity to motivate them to change their lifestyle and ultimately to help them prevent the disease.*"[40]

This is a poor approach to improving the health of populations, because it is not the case that common diseases only occur in people at high genetic risk. For a given common disease, most cases will not occur in the high-risk group, however it is defined, but in the majority of people at close to average risk. Thus, it is impossible to make a major impact on prevention without using public health measures that help the whole population, not just those in the high-risk group.[41] This is particularly the case for diet-related diseases and conditions, such as obesity, type 2 diabetes and high blood pressure, which have major impacts on health in the general population in the US and the UK, and many other countries. Targeting lifestyle advice at a small group of people does not make sense because most people (not just 5% or 10%) need to improve their diets in these countries. For example, a heart-healthy Chinese diet could make a major difference to the more than one-fifth of the world's population that consumes Chinese cuisines regularly.[42]

Thus, the idea of genetic 'prediction and prevention' acts as a major distraction from population policies that might make a difference, such as helping people to quit smoking, reducing sugar and salt in processed foods, or tackling poverty, air pollution, or access to green spaces. This helps to explain why, historically, the genetic approach to prevention of common diseases, such as lung cancer, heart disease, hypertension and type 2 diabetes, has been supported by companies selling cigarettes and unhealthy, processed foods.[43,44] These companies and the scientists that worked for them exaggerated the predictive power of genetic tests to imply that only people who were genetically susceptible would develop lung cancer or diet-related diseases if they smoked or ate foods high in salt or sugar, so the rest of the population could continue smoking or eating unhealthy processed foods. This isn't true, so this approach to disease prevention does not make any sense.

A specific example shows that in the case of type 2 diabetes, knowledge about genetic susceptibility has no implications for decisions about who should be targeted for intensive lifestyle interventions.[45] The risk due to obesity is much more important and therefore universal approaches to reduce excess weight are needed, regardless of the genes a person has.

Even if PRSs identified high risk groups correctly, and targeting behavioural changes at such groups was a good idea, there is little evidence that genetic test results help to sustain positive behavioural change.[46,47] Causal beliefs about genetics can influence people's responses to genetic information, and many studies suggest that people perceive conditions as less controllable when portrayed as caused by genetics as opposed to lifestyle or

environment.[48] This could potentially lead to someone becoming more fatalistic and less motivated to make lifestyle changes. A more recent study, discussing the hypothetical return of PRSs to a group of patients in primary care, found that many had a lack of trust in the results, unless corroborated by additional information, and that PRSs by themselves would be regarded by these patients as insufficient to trigger preventive interventions.[49]

More broadly, individualised approaches to disease prevention fail to take account of the escalating rates of avoidable ill health, planetary damage, and social and health inequity now referred to as the commercial determinants of health. One recent analysis notes that just four industry sectors (i.e., tobacco, ultra-processed food, fossil fuel, and alcohol) already account for at least a third of global deaths, and that the power of some commercial interests makes it harder to pass policies that would protect human and planetary health.[50]

In addition, poorer people are generally at higher risk of most common diseases, and measures to tackle health inequalities and poverty in childhood are therefore key to achieving better public health.[51,52,53,54] Social determinants of health affect mental as well as physical health.[55] Major factors that contribute to the risk of common diseases include environmental factors, as well as socio-economic factors. For example, almost the entire global population (99%) reportedly breathes air containing pollutants that exceed World Health Organisation (WHO) air quality limits.[56,57,58,59] Climate change also threatens health, in some countries more than others.[60] The importance of identifying social and environmental risk factors is that (unlike a person's genome) they can be modified, thus reducing cases of disease.[61]

In summary, the idea of using PRSs to target lifestyle advice is a distraction from tackling environmental and socio-economic causes of disease. There is a risk that they do not empower people (as claimed by the companies involved), but disempower them, by making them believe the most important risk is in their genes.

5. Should PRSs be used to decide who takes extra tests or medicines?

"*Contrary to what many people might expect given usual deterministic discourses around genomics, a high polygenic score will generally have a rather underwhelming impact on absolute risk and both clinicians and the public need to know this*." Medical researchers writing in the British Medical Journal, 2023.[62]

Although it makes no sense to target lifestyle advice to small high-risk groups, it could be argued that it does make sense to target medication or further testing at such groups. This is because there are downsides to taking medicines and unnecessary tests, so they cannot be rolled out to the whole population without causing harm. However, it can also be argued that PRSs are, in themselves, also unnecessary tests, which can cause harm to people taking them. Part of this debate relates to the predictive value of PRSs and whether they can improve health outcomes, as discussed below.

There are still major disagreements about how good PRSs are at identifying high risk groups, and whether they are really useful. A key question is whether the idea of targeting medication at a small group of people at the highest genetic risk (e.g., the top 3% or 5%) is really good for health. Doubts about this strategy relate to the poor predictive value of PRSs, and the large uncertainty in the predictions made for individuals. Box A describes some of the ways in which the predictive value of a PRS can be measured. Clearly, if a test has poor predictive value, it is unlikely to be useful. However, it should be noted that a high predictive value is not necessarily sufficient to justify the use of a PRS, or any other medical test, in

healthcare: its clinical utility (i.e., whether using the test to make decisions actually improves health outcomes) and cost-effectiveness also need to be assessed.

In general, causal risk factors are poor predictors of disease, because while many people are exposed to them only a few people develop the disease.[63] This is the case even for important causal factors such as smoking. For example, the lifetime risk of lung cancer in smokers is only about 1 in 10 (meaning most smokers do not develop it), but if everyone stopped smoking, more than 85% of cases of lung cancer could potentially be avoided.[64] In contrast to smoking, and other social and environmental factors, a person's genetic make-up can't be changed. Thus, measuring genetic factors is inherently less useful to an individual, unless a medical purpose can be demonstrated.

Box A: Measuring the predictive value of PRSs

There are a number of ways of assessing how well a medical test works. How good a test needs to be will depend on the context in which it is used. For example, it might be important to identify everyone with a given disease, but inadvertently include some people who don't have it; or, it might be better to be highly certain that the people identified have the disease, at the risk of missing some cases.

The performance of predictive tests, such as a PRS for a particular disease, can be measured in several ways, which each have their pros and cons.[65,66]

A predictive test's sensitivity is its ability to correctly identify those who will get the disease and its specificity is its ability to correctly identify those who won't get the disease. There is usually a trade-off between a test's specificity and its sensitivity: a test which is highly specific (so it only identifies people who will develop the disease) is often not very sensitive (it misses many potential cases of disease, giving these people 'false negative' results), and vice versa, a test which is highly sensitive (so it picks up all potential cases of disease) is not very specific (identifying many people who would never develop the disease, so-called 'false positives').

The most common measure of test performance is known as the Area Under the Curve (the AUC). This is worked out by drawing a graph of the sensitivity against 1 minus the specificity (i.e. the false-positive rate) of the test: this graph is known as a receiver-operating characteristic (ROC) curve. How well the test works (which depends on both its sensitivity and its specificity) can then be measured by calculating the area under the curve (AUC) of the ROC curve. The AUC is the probability that a randomly selected affected individual will have a higher screening test value than a randomly selected unaffected individual. If a predictive test was perfect in predicting who would get a disease and who would not, the AUC would be 1; if it was no better than guessing who would get the disease, it would have an AUC of 0.5 (in this case, the test is useless). In reality, the AUC is somewhere between these values, with a higher value meaning a better predictive value. For example, in one study a simple risk prediction model for cardiovascular disease (based on information such as age, blood pressure, body mass index, whether a person is being treated for diabetes or hypertension, and their smoking history), with no genetic information or laboratory measurements, has an AUC of 0.749 for men and 0.785 for women, and this can be improved to 0.763 for men and 0.793 for women by adding information about cholesterol levels.[67] There are limitations to the use of the AUC because only the ROC curve itself shows the full relationship between the sensitivity (or detection rate) of the test and its false-positive rate (or 1 minus the specificity). The same AUC can therefore reflect different screening performances and a better alternative would be to report the detection rate of the test for given false-positive rates, or false-positive rates for given detection rates.[68]

The C-statistic (or C-index) is another measure of performance, which is the same as the AUC for a binary outcome (getting a disease or not, for example). However, if instead the time to getting a disease (or survival time) is important, different AUC's must be plotted for different times, and the C-statistic is not the same as the AUC. As for the AUC, the higher the C-statistic, the better the model can discriminate between subjects who experience the outcome of interest and subjects who do not.

The Net Reclassification Index (NRI, also known as the 'Net reclassification Improvement') is a different measure, which is commonly used to look at the slightly different question of whether adding new information changes whether a given individual is thought to be at high risk of a disease. For example, if people are already classified as high and low risk of cardiovascular disease based on a prediction of risk (using information such as age, body mass index, smoking status, cholesterol levels and blood pressure), the NRI is a measure of the proportion of people whose risk is reclassified when new information (such as a PRS) is added (to create what is known as an Integrated Risk Score, IRS, or Integrated Risk Tool, IRT). NRI values above 0.6 are considered strong, around 0.4 are intermediate, and below 0.2 are considered weak.[69] The NRI is intended to measure whether people are correctly reclassified by the new model. However, some researchers argue that the NRI can be artificially inflated and hence misleading when multiple markers that are not predictive are included in a risk prediction model.[70] These researchers suggest that the NRI statistic calculated on a large test dataset using risk models derived from a training set is likely to be positive even when the new marker has no predictive information, and that an incorrect risk function that includes an uninformative marker can erroneously yield a positive NRI. A recent review has concluded that NRI statistics are unhelpful (at best) and misleading (at worst), with problems that include unacceptable statistical behaviour, incorrect statistical inferences, and that they lack any clear interpretation.[71]

The NRI is intended to measure the marginal strength of the new predictor but the ROC (usually summarised in a limited way, by the AUC, as described above) is intended to measure the overall predictive value of the model including all risk predictors. Although it is often thought that combining risk factors can substantially improve screening performance, this is not usually the case.[72] The increase in screening performance when new risk factors are added is usually more modest than expected, especially if the detection rate of each risk factor, for a given false-positive rate, is low. An online tool is available to aid in assessing whether a risk factor might be a worthwhile screening test.[73]

The positive predictive value (PPV) is the ratio of patients truly diagnosed as positive to all those who had positive test results. For a predictive test, it is the proportion of people predicted to get the disease who actually go on to develop it.

Many recent studies claim that PRSs now have sufficient predictive value to be considered for use in health services. However, these claims have often been exaggerated. An assessment of the use of performance measures, such as the AUC and NRI, used to evaluate PRSs, criticises researchers' understanding of these measures, and finds that even small insignificant changes in the AUC are often interpreted as indicating improvement when the NRI is statistically significant.[74] This study assessed 32 studies, most of which evaluated cardiovascular and cancer prediction. The researchers conclude that small improvements in the predictive ability of PRSs are being overinterpreted, and this is not likely to improve health outcomes. The claims made for PRSs are discussed in more detail below.

5.1 PRSs as stand-alone tests

A 2019 review of 3,700 GWAS concluded that most SNP-derived genetic risk predictions are not as good as existing clinically based disease risk predictors.[75] It found that the average

GWAS produces a multi-SNP risk predictor with an AUC of 0.55, which is not much better than random guessing. In a more recent example, a polygenic risk score for type 2 diabetes was estimated to have an AUC of 0.659 in people categorised as being of European ancestry, with lower values in other populations (down to 0.568 in populations categorised as African).[76] A subsequent PRS has a similar AUC of 0.66 in a population classed as European and 0.58 in the population classed as African.[77] In contrast, clinical risk predictors in use in medicine tend to have AUCs of more than 0.7 or 0.8. Higher AUCs have been reported for some PRSs, but only when the score has been adjusted for age and sex, a practice which means the AUC is actually being reported for a combined risk score (including the PRS plus age and sex). Because age and sex often predict the risk of a disease quite well, this means that the reported AUC does not measure the predictive value of the PRS. For example, an AUC as high as 0.81 was reported for Coronary Artery Disease in one study, when the most plausible estimate was that the true AUC based on SNPs alone was only 0.65.[78,79] In a study by the Australian company Genetic Technologies, AUCs were much lower for PRSs alone than for PRSs plus sex and age: for coronary artery disease the AUC for the PRS alone was 0.587 (compared to 0.706 when age and sex were added), for hypertension 0.566 (compared to 0.677), atrial fibrillation 0.613 (compared to 0.738), stroke 0.512 (compared to 0.668), and type 2 diabetes 0.595 (compared to 0.638).[80] In this study, increasing the number of SNPs did not significantly improve performance (for example, for atrial fibrillation, the PRS using 265 SNPs had an AUC of 0.599, whereas the PRS using 216,837 SNPs had an AUC of 0.613). A database of PRSs is now available, where the AUCs from some studies are available (although the website warns that these have not been checked independently).[81]

In another example, a study published in 2020 found that a PRS for coronary heart disease (CHD) did not significantly improve the discriminative accuracy (measured by the AUC, or C-statistic), or Net Reclassification Index (NRI, see Box A), compared to existing risk predictors.[82] This study used the best-performing PRS available (based on more than 6.6 million SNPs).[83] It concludes that this PRS "*offered little to no improvement in CHD risk stratification*" in the population studied, as the score minimally changed risk discrimination and reclassified fewer than 10% of individuals to a higher or lower CHD risk category. Studies which combine PRSs with other risk factors are considered in more detail in the discussion on Integrated Risk Scores (IRSs), below.

For cancers, not only are the AUCs for current PRSs are too low to be useful in disease prediction (ranging from 0.53 to 0.67), the theoretical best scores if all the relevant SNPs were to be discovered is predicted to continue to be low (0.64 to 0.73).[84] For schizophrenia, a PRS developed and tested in a Danish sample had an AUC of only 0.62, which does not support its use as a predictive test.[85] This PRS also failed to identify the subset of patients with treatment-resistant schizophrenia.[86] A more recent study reports an AUC of 0.74, but the authors conclude that this is insufficient for predicting schizophrenia in the general population.[87] In another example, a recent study of dementia found that the predictive value of a Genetic Risk Score (GRS), developed from genetic variants with genome-wide significance, depended largely on the population in which the GRS was tested, with the C-index for developing Alzheimer's Disease over the next 5 years varying widely between 0.587 and 0.952, adjusting for age, sex, principal components and APOE alleles.[88] This suggests that the predictive performance (which is in any case inflated by the inclusion of age, sex and other information in the score) is not reliable. Further, the increase in C-index due to adding the GRS to the other risk factors is very small (0.002 on average for the 5-year predictions). For comparison, a dementia risk score developed in UK Biobank without using any genetic information reportedly achieved a C index (AUC) of 0.86 for men and 0.85 for women to predict the individual 5-, 9-, and 13-year dementia risk.[89] Socioeconomic adversity (unemployment and low educational level) and comorbidities (respiratory, cerebrovascular and cardiovascular disease, diabetes and hypertension) were the most

important modifiable risk factors in this study. However, subsequent studies suggest that such risk scores are of limited value in targeting people for dementia prevention.[90]

Genetic tests to predict drug response (efficacy, dose or adverse drug reactions), known as 'pharmacogenetic' or 'pharmacogenomic' tests, are not the main topic of this report. However, it is worth noting here that PRSs for drug response also perform poorly and are often inconsistent.[91]

5.2 Using PRSs to target individuals in the high-risk group

"…*when polygenic risk scores were applied to five isolated diagnoses, 20% of the population was found to be at "high risk" for at least one of them. If such algorithms are applied to many diagnoses, everybody is likely to be labelled at high risk of something*". Researchers in Norway and Denmark, 2023.[92]

In response to the evidence that PRSs have poor predictive values as measured by AUCs, the advocates of using PRSs have tried to improve their predictive value by including more SNPs. In addition, they have also made a number of arguments that the AUC is not the right measure of how useful the PRSs really are. This generally means arguing: (i) that PRS should not be used as stand-alone tests, but combined with other risk factors into Integrated Risk Scores (IRS), and/or used to categorise people into groups prior to using other screening tests; and (ii) that they are mainly useful for identifying the small proportion of the population at highest risk, so that medicines and lifestyle changes can be targeted at them. Thus, they argue that the success of the predictions should be measured by the Net Reclassification Index (NRI), despite some serious criticisms of this method (see Box A).

In this subsection, we first consider the implications of using PRSs to identify a high-risk group (this is variously defined as the 1%, 5%, 10% or 20% of the population with the highest risk score, calculated using a stand-alone PRS or an IRS, which includes the PRS plus other known risk factors). First, it is important to note that in order to implement this strategy it is possible that the whole population will still need to have their genomes screened. Alternatively, only a subset of the population (those at borderline risk calculated using other risk factors) might be selected to have a PRS.

For example, in the UK, the company Genomics PLC states on its website that it will "*empower everyone*" to make "*genomically-powered decisions for longer, healthier lives*".[93] Genomics PLC is aiming to deliver its tests initially through healthcare services (the NHS in England, and private healthcare in the USA), although it has not ruled out also selling tests directly to consumers. The company's 'White Paper' on Polygenic Risk Scores states, "*Polygenic risk scores are not stand-alone diagnosis tools. They complement existing risk factors to improve screening programmes by better targeting at-risk individuals. They can also be used to better interpret screening tests*", and "*For many diseases improved prevention is possible for those individuals at high risk through either lifestyle changes or medical intervention*".[94]

Although Genomics PLC sounds relatively cautious about the predictive value of individual PRSs, this company still argues that everybody in the whole population should take such tests to identify for which diseases they are in the 'high genetic risk' group.

In 2019, Genomics PLC had worked on 16 diseases, with plans for many more.[95] If we assume the genetic risk of each disease is independent, more than half the population (56%) would be in the top 5% for at least one of these diseases.[96] If the number of diseases for which PRSs were available increased to 50, say, more than 9 in 10 (92%) would be in the top 5%. This is consistent with evidence provided by Professor Peter Donnelly, now

CEO of Genomics PLC, to parliament in 2008, "*For a particular disease, and a typical individual, their genetics is unlikely to have a major impact on their disease risk. Put another way, these genetic markers are not yet good predictors of disease outcome, as has been widely noted. But there is another perspective…*
From an individual's point of view, for most diseases the genetic risk is about average, but over 50 or more diseases the chance of being in the top 5 per cent for one or more is 95 per cent. So, a potentially helpful perspective on "consumer genomics" is that for the individual it can identify the small subset of diseases for which their genetics puts them at much increased risk."[97] This idea was repeated in Genomics PLC's written evidence to the same committee in 2019, "*For any particular disease, a clinically meaningful increase in disease risk predicted by PRS typically will only apply to a few percent of individuals (although as for coronary artery disease, in a large population, this information can direct treatment to hundreds of thousands of individuals). Critically, while most individuals will have average risk for any particular disease, it is very likely that they will be at the extreme of genetic risk for at least one disease*".[98] In 2022, Genomics PLC announced that it had now developed PRSs for 28 diseases.[99]

Thus, nearly the whole population could be identified as at 'high genetic risk' for at least one disease by using PRSs for multiple diseases, meaning they could be eligible for preventive treatment, perhaps from an early age. Enthusiasts argue that this could lead to early treatment of people identified as at risk but who are not yet ill. However, there is also a danger that this leads to over-treatment of people who would never have got the predicted disease.[100] Identifying everyone as potential patients before they become ill could lead to a massive expansion in the market for medicines and other products (such as supplements, foods and other 'wellness' products or services) to people who have no symptoms of disease. This might be good for pharmaceutical companies and others marketing such products, but would it really be good for health? This depends partly on what treatments are available (and their side effects) but also on how good PRSs are at predicting which people will develop a particular disease.

Genomics PLC provides three graphs in its 'Polygenic Risk Scores' white paper, all taken from published scientific papers.[101,102,103,104,105,106] These papers are all based on data from subjects considered to be of 'European ancestry'. This is a very important limitation and is discussed in Sections 7 and 8. Considering only the results for this 'European ancestry' group for now, the graphs show how the PRSs for breast cancer (women only), coronary artery disease (men only) and prostate cancer (men only) work in the sense that the 3% of people in the group calculated to be at highest genetic risk are more likely to develop the predicted disease than other groups. However, the graphs also show that most people given a high risk PRS score will <u>not</u> develop the predicted disease by the age of 75, even if the predictions are reliable. According to these graphs, for breast cancer about 1 in 4 (25%) of women given a high risk PRS score get breast cancer by the age of 75; for coronary artery disease, nearly a third of men (about 30%) given a high risk PRS score get this disease by the age of 75; and for prostate cancer, just over a quarter (more than 25%) get this condition by the age of 75. According to these calculations, for breast cancer and prostate cancer the predicted risk is about 3 times higher in the 'high genetic risk' group than in the 'average genetic risk' group and for coronary artery disease it is about twice the risk. However, most people in the 'genetic high risk' group will still not get the predicted disease. This means there is a risk that people in this group could be treated with (or sold) medicines or other products to supposedly prevent diseases that they're never going to get. A recent UK study found that more than 66% of people over 70 have an underlying health condition.[107] Thus, these findings do not mean that most people over 75 are healthy, just that most would not develop the disease identified by the PRS, and hence they would likely receive preventive treatment for the wrong disease. The impacts of this on a person's health would vary depending on whether the intervention had any side effects or other adverse consequences.

There would also be major implications (including costs) for health services and society more broadly (see Sections 8 and 11).

Equally important is that fact that most cases of each disease do not occur in the 'high genetic risk' group but in the majority of people in the groups who are classified as at lower genetic risk. For each condition in this report, Genomics PLC makes much of the fact that people in the "high risk" group (defined as the 3% of people at highest risk) are around 2 to 3 times more likely to develop the disease than those in the "average risk" group. However, this is actually a sign of poor predictive value: much higher differences in risk (greater than 10-fold) are typically required to substantially improve predictions.[108] Thus papers that simply report odds ratios of 2 or more for people in the 'high risk' tail of the distribution of the PRS for various diseases (such as a recent study in US veterans[109], and a study advocating the use of a breast cancer PRS by the US company Myriad Genetics[110]), without reporting other measures such as the ROC and the AUC (as described above), are not providing the full picture, because such tests are likely to have poor predictive value. Odds ratios typically compare risks in the tails of a single risk distribution with the risks in the rest of the population, but these ratios ignore the proportions of individuals who will or will not develop the disease that fall in the region between the tails of the distribution. In general, most cases of common disease in a population will not occur in the high-risk group. This means that what appears to be a strong risk factor can still be a poor screening test, because it misses most cases, or, alternatively identifies too many people as at risk who would not develop the disease. An important paper by experts in public health notes, "…*it is not well recognized that estimates of the relative risk between a disease marker and a disease have to be extremely high for the risk factor to merit consideration as a worthwhile screening test. To our knowledge, no genome-wide polygenic score meets this requirement, and none is likely to do so with polygenic scores that emerge in the future. It is important that the potential applications of genomic medicine are not compromised by raising unrealistic expectations in medical screening*".[111]

A similar vision to that of Genomics PLC is provided by the US company Allelica, which has published a paper (not yet peer reviewed) on the use of PRSs with the tile 'Software as a Service for the Genomic Prediction of Complex Diseases'.[112] This paper provides the results of PRSs for coronary artery disease (CAD), breast cancer, and prostate cancer and states that additional PRSs have been developed for other diseases such as atrial fibrillation, type 1 and type 2 diabetes, hypertension, inflammatory bowel disease and coeliac disease. Although the paper reports a relatively high AUC of 0.81 for its PRS for CAD, a closer examination reveals that this is calculated after adding age and gender to the risk predictor: the AUC for the PRS alone is only 0.65 (Figure 15 of the paper). The AUCs for breast and prostate cancer are also inflated by age (0.68 and 0.8), with the true values for the PRSs alone not reported in the paper. The positive predictive value (PPV) for people in the top 3% of genetic risk for each of the diseases is given for the most predictive PRS as 13.36% (0.136) (CAD), 20.20% (0.2020) (breast cancer) and 19.8% (0.198) (prostate cancer). Thus, only around 1 in 5 of the people in the high genetic risk group will develop the predicted disease. As discussed above, a low PPV could mean that many more people are given preventive treatment than would have developed the predicted disease. The consequences of this depend on the proposed intervention for those in the high-risk group.

If an intervention is very safe and effective it might not matter that many more people are treated than develop the disease: however, in such cases it may also not be worthwhile trying to limit the intervention to those at highest risk (usually at the cost of missing most cases of disease), or defining the high-risk group other than by age (which may predict the risk of developing many common diseases sufficiently well). If, on the other hand, an intervention may be harmful, it may not be appropriate or safe to offer it to many more people than are expected to develop the disease: in this case a test with a very high PPV is needed. In addition, for some conditions, preventive options may be limited, or (as with

lifestyle changes or the prevention of pollution), may important for everyone, not just those in the high-risk group.

It is also critical to be aware that 'high' and 'low' genetic risk is not the same as 'high' and 'low' overall risk for a particular condition. For conditions such as type 2 diabetes and coronary artery disease, non-genetic risk factors are much more important: "*As a result, it can occur that an individual feels protected due to a low genetic risk score, despite being at high risk due to being a heavily overweight smoker, when PGS are reported without consideration of other risk factors*".[113]

The papers cited above only show that people in the 'high genetic risk' group for a particular disease are on average more likely to develop the disease than those in the 'low genetic risk' group. In other words, PRSs are used to categorise people into groups which differ in their risks (i.e., this is 'categorised medicine' not 'personalised medicine', despite the fact the latter term is often used). Predicting outcomes for individuals is much less precise than for populations because stochastic processes (i.e. random processes and unobservable events) will always play a large role in shaping individual outcomes (this issue is discussed further in Section 7).[114] Thus, 'high' and 'low' categories of genetic risk can be largely meaningless to the individual. In addition, trust in the predictions could be undermined if confidence in the 'high' and 'low' risk categories is low. This is discussed in the next subsection.

5.3 Are the high-risk categories reliable for individuals?

"…*for each disease, of those classified in the top 5% of risk by the first PRS, over 60% were not so classified by the second PRS. We found substantial discordance between different PRS for the same disease, indicating that individuals could receive different medical advice depending on which PRS is used to assess their genetic susceptibility*". [115] Scientists at Oxford and Harvard universities, September 2022.

The above discussion assumes that polygenic risk scores correctly assign the right people to the high-risk group. In reality, different PRSs will give very different answers to the question of whether a given person is at high genetic risk, as discussed below. This means individuals cannot know with any confidence that they have been allocated to the right category of genetic risk ('high', 'medium' or 'low'). Research suggests that many patients may be sceptical of genetic risk predictions and that, if they don't trust the predictions and recommendations they are given, they may not be willing to take extra tests and treatments based on their PRS results.[116]

A study assessing the value of a PRS for coronary heart disease (CHD) screening (discussed above, for its conclusion that the PRS offered little improvement to risk stratification) also found that, "*among individuals who subsequently developed CHD, the specific group that screening programs wish to identify, the majority of reclassifications (79%-80%) were incorrect*". [117] Another study looked at three different PRSs for breast cancer (one developed in the UK, one in Estonia, and one combining both) and found poor levels of agreement between the different PRSs. Only 0.33% of women in the study were categorised in the top 5% of genetic risk with all three scores, compared to about 10% of the women who were categorised as at high genetic risk by at least one of the different PRSs.[118]

A more recent study looks at this problem in more detail.[119] The authors compare two different published PRSs for three different conditions (breast cancer, hypertension and dementia), in the subset of people categorised as 'white British' in the UK Biobank (for a discussion of the implications for other groups, see Sections 7 and 8). All the PRSs had relatively low predictive value as measured by the AUC (as described above), although this did improve slightly in the second (later) PRS for each disease (from 0.63 to 0.64 for breast

cancer; from 0.57 to 0.59 for hypertension; and from 0.55 to 0.57 for dementia). (It should be noted that the dementia PRS excluded the role of genetic variations in the APOE gene, which are known to have a relatively large effect on risk). However, the authors were surprised to find that less than 80% of SNPs in the first PRS were represented in the second PRS, for all diseases. More importantly, there was a substantial reclassification of predicted risk. For example, of the women in the top 1% of breast cancer risk using the first PRS, only 23.1% were still classified as in the top 1% of risk by the second PRS. For participants categorised in the top 5% of genetic risk by the first PRS, only 35.7% (for breast cancer), 35.8% (for hypertension) and 40% (for dementia) were categorised as in the top 5% using the second PRS for each disease. This means that treatments or recommendations made by a doctor would be very different for the same individual depending which PRS was used. The authors of this study conclude that "*such an arbitrary element in health care is obviously undesirable*". They do not reach firm conclusions about why the misclassification happens, but note it is not only due to the inclusion of different SNPs, but also to the use of different methods in the calculations (problems with some of the assumptions made when writing these computer algorithms are discussed in Section 7).

The authors of this paper also note that the portability of the PRS depends on characteristics of the population studied, such as economic status, age or sex, and that variations they observed for the different PRSs are "*far from the "fixed" or "one-time" value at birth that is often assumed for PRS*". Thus, further doubts about what PRSs mean for individuals concern the fact that, although a person's genome doesn't change, their genetic risk can change with time and depends on the environmental context (see also Section 7). Even for relatively rare mutations, such as those in the BRCA2 gene which lead to a high risk of breast cancer, a study in Iceland found that the risk associated with the same mutation can change significantly over time (in this study, the cumulative incidence of breast cancer before age 70 years in mutation carriers increased from 18.6% in 1920 to 71.9% in 2002).[120] More recently, a large study in UK Biobank has found a tendency for genetic relative risk to change significantly (usually to decline) with increasing age.[121] One study has attempted to separate the effects of date of birth (used as a proxy for changing environmental exposures in a population over time) from the effects of age on PRSs.[122] This study found that the effect of year of birth was substantial, suggesting that differences in environmental exposures (related to a person's year of birth) could be a major source of poor replication of PRSs. This creates two problems: firstly, significant doubts about how PRSs are calculated (discussed further in Section 7); and secondly, problems with interpretation by doctors and their patients.

One study, which only includes the uncertainties due to imperfect data, calculates error bars (95% confidence intervals) around individual PRS estimates for people categorised as 'white British' in UK Biobank (the implications for other populations are discussed in Sections 7 and 8).[123] This study finds that the most of the categories are highly uncertain, by which they mean that it is not possible to be 95% certain that the individual is correctly categorised into a high, low or medium genetic risk group. For example, for Body Mass Index (BMI, a measure of whether someone is overweight or obese), only 6.2% of people in the top 10% of genetic risk could be attributed to that group with 95% certainty, whereas for cardiovascular disease (CVD), none of the attributions to the high genetic risk group could be described as certain.

A more recent study also reports a very poor level of agreement between different PRSs for cardiovascular disease.[124] These results again show that different individuals will be given statins, depending on which PRS is used. This study looks in more detail at the question of why different PRSs give different answers, and finds that both measurement error (stemming from using a finite number of samples) and different construction methods (i.e. how the data is combined in a computer algorithm) play an important role. This is discussed further in Section 7.

Another major problem is that the predictive value of PRSs drops when they are applied to different populations. Even within Europe, the performance of PRSs drop significantly when applied to different European populations.[125] In this study, as well as a drop in the AUC for nearly all models (developed in Germany, Estonia and the UK) when applied to different data sets, in some cases the 'high genetic risk' category did not in reality reflect a higher occurrence of coronary artery disease. This has important implications for individuals, as the genetic risk category they are given becomes even less reliable. This issue, including the implications for minoritised ethnic populations, for whom predictive value may be poorer, is discussed further in Sections 7 and 8.

These severe problems with PRSs are exacerbated by poor understanding of what the scores mean and their limitations. In one study, of the users of Impute.me, a website which allows people to upload genomic data obtained from other companies (which has since been acquired by Nucleus Genomics), only 25.6% of participants correctly answered all questions assessing understanding/interpretation of PRSs, with many misinterpreting their risk.[126,127] Another study found that many patients, and even some primary care physicians, interpreted being told that their genetic risk was at the 98th percentile for a condition (meaning they are predicted to be in the 2% of people at highest genetic risk) as meaning that they were at 98% risk of the condition (many times higher than their actual risk would be).[128] This study, which was conducted for the US eMERGE network, which plans to return PRSs to patients, also found that measures of relative risk, such as odds ratios, were often misinterpreted. A change in relative risk (in one group compared to another) may still mean a low absolute risk, which is insufficient to warrant any further testing.[129] Both patients and physicians had a strong preference for absolute risk information, and for information regarding how important the genetic component of the risk is compared to other factors.[130] This study also highlights the dangers of reporting results separately by population group (race/ethnicity or genetic ancestry), noting that many individuals do not fit neatly into any of the groups, whilst some will fit into more than one group (see Sections 7 and 8).

5.4 What do PRSs mean for families?

Rare genetic disorders are often caused by a mutation in one gene. Although new mutations can arise by chance, many are inherited. Such rare disorders follow a pattern in families according to whether the mutation in the gene is dominant (only one copy from one parent is needed to inherit the condition) or recessive (two copies must be inherited before the child shows symptoms of disease). Thus, having a genetic test for one of these disorders can also reveal that family members may be at risk, and sometimes reveal non-paternity (if the supposed biological father does not have the required mutation to cause a recessive genetic condition). Familial forms of common diseases, such as breast cancer caused by (dominant) mutations in the BRCA1 or BRCA2 genes, also run in families, although not everyone with these mutations will develop the disease. Thus, these types of genetic tests may have implications for other members of a person's family.

Although common, complex diseases, such as heart disease or most cancers, can also occur several times in the same family, this is not necessarily due to shared genetic factors. Common diseases can be expected to occur several times in the same family simply due to chance, or because families often share some of the same habits (smoking or unhealthy diets), environments (living in a polluted area) or socio-economic circumstances (such as poverty, poor housing, and limited educational opportunities), which may increase their risk of common diseases and related conditions, such as obesity.

Several studies have attempted to assess to what extent PRSs for complex diseases explain a family history of those diseases. In heavy smokers at risk of lung disease (chronic

obstructive pulmonary disease, COPD), one recent study found the PRS for COPD explained 16.5% of the effect of family history in participants classed as 'non-Hispanic white', and only 3.1% in participants classed as 'African American'.[131] The authors conclude that a substantial component of the effect of family history on COPD could be due to shared environmental factors. This finding is similar to one for schizophrenia, which reported that 17.4% of the effect of family history on schizophrenia was mediated through the PRS.[132] In two studies, PRSs for coronary heart disease were found to be independent of family history, suggesting they did not explain the clustering of this disease in families at all.[133,134] High PRSs for coronary artery disease, atrial fibrillation, diabetes are more likely to be shared by siblings than would occur by chance: however, differences between siblings in polygenic scores play only a modest role in which sibling develops the disease.[135]

If PRSs do not have significant implications for the health of family members this may ease some privacy concerns (although relatives and non-paternity can still be identified through this type of genetic test, see Section 11). However, if PRSs explain little of the clustering of diseases within families, this raises further questions about what they mean for individuals, and could conflict with the expectations of the people taking them.[136]

5.5 Use of PRSs with other risk factors in Integrated Risk Scores (IRS)

"*Overall, it is clear that there is some, but limited, added value of PGS on top of questionnaire-based risk factors for predicting T2D* [Type 2 Diabetes] *and CAD* [Coronary Artery Disease] *incidence compared to when only free to attain risk factors are used. However, PGS are costly, logistically complex and is time consuming compared to the questionnaire which is cheap, fast and easy*."[137] Researchers based at Groningen, The Netherlands, 2023.

Due to the poor predictive value of PRSs alone, commercial companies have started to propose that they are combined with other clinical risk factors to create Integrated Risk Scores (IRSs). The idea is that the IRS will lead to some people being moved from a borderline risk group (calculated using clinical risk factors without genetic information) into a high-risk group, due to the additional information from the PRS, making them eligible to receive a treatment (such as statins to reduce heart disease risk), or screening tests (e.g. for a particular type of cancer) that they would n ot otherwise have had. Other people will move from the high-risk group (based on clinical risk factors) to a lower risk one once the PRS is added. However, advocates do not always argue that this group should no longer be eligible for treatment or screening.

The main area of research for IRSs has been cardiovascular disease, because risk scores based on clinical risk factors (such as cholesterol levels) are already used routinely for prescribing statins in many countries. For example, the UK National Health Service (NHS) is now piloting the use of a PRS for heart disease from the commercial company Genomics PLC, combined with a risk score based on traditional risk factors such as blood pressure, smoking history and cholesterol.[138,139]

One reason the use of Integrated Risk Scores (IRS) has been questioned is because of the possible risk of 'double counting'. It is possible that some of the SNPs in a PRS for cardiovascular disease are associated with measured risk factors such as high blood pressure or cholesterol, and these effects are therefore counted twice, through the clinical risk factors included in the IRS, as well as in the PRS itself. Some argue that, in an IRS, the PRS should only include the genetic contribution that is <u>not</u> captured by the clinical risk factors.[140] However, if this were done, the PRS could have even less predictive value and be less cost-effective, raising further doubts about whether its use is actually worthwhile. Similarly, if environmental factors are included in an IRS (including lifestyle factors such as

diet or smoking), there is a risk of introducing bias due to unknown correlations between genetic and environmental factors.[141] On the other hand, if genetic risk factors do not correlate with non-genetic ones, but non-genetic ones are more important, people might be misled about their risk if this is based on a PRS alone. A recent paper argues that non-genetic risk factors, such as body mass index (BMI), sex and smoking status should be combined with PGSs to improve risk predictions, but the results in this paper show that PGSs for type 2 diabetes and coronary artery disease add little to the predictive value (measured by the C-index) compared to risk assessments based on questionnaire-based risk factors alone.[142] A more fundamental question (discussed further below) is why the UK National Health Service (NHS) is piloting an approach that is unlikely to improve screening performance or health outcomes, which depend on reducing (rather than quantifying) risk.[143]

In contrast to the claims made by commercial companies, a recent review of incorporating PRSs for coronary heart disease into an integrated risk score (IRS) concludes, "*the addition of PRS to traditional risk scores does not appear to provide meaningful improvements in clinical decision-making in primary prevention populations*".[144] This review of 5 major published studies concludes that the incremental improvement of adding the PRS to a standard risk factor model for coronary heart disease ranged from "*absent in some studies to small in others*". As well as low C-statistics (ranging from 0.549 to 0.623 for the PRS alone), this study finds very small increases in the C-statistic when the PRS is added to a standard risk factor model, and low net reclassification index (NRI). This paper also considers the later publications by Genomics PLC and by a large-scale study in China, and finds that they have similar limitations. Another study has confirmed only a small change in C-statistic when a PRS for coronary artery disease is added to existing risk predictions based on clinical risk factors (the 'pooled cohort equations' model, or the QRISK3 score used in the UK).[145] This paper notes that earlier findings, advocating the use of PRS, either did not compare them to clinical non-genetic risk predictions (due to the lack of cholesterol measurements in those studies), or used a poor non-genetic model as a baseline (for example, with a low C-statistic of only 0.67, compared to the C-statistic of 0.76 obtained with the pooled cohort equations in this study). A further study comparing a PRS for long-term risk of coronary heart disease with risk predictions using traditional risk factors found that the change in the C-index when the PRS was added to the traditional risk factor score was only 0.03, 0.02, and 0.002 in young, early-midlife, and late-midlife participants, respectively.[146] The authors conclude that, "*PRS, an immutable factor that cannot be directly intervened on, has minimal clinical utility for long-term CHD prediction when added to a traditional risk factor model*". A 2023 study similarly found that the C-statistic for a PRS for CHD was only 0.69, and that the change in C-statistic when it was added to a score based on traditional risk factors (with a C-statistic of 0.76) was only 0.02.[147] In this study, the NRI was also not statistically significant, and adding an alternative risk predictor (coronary artery calcium score) made more difference to the risk predictions.

In contrast, in a press release in 2021, Genomics PLC claimed that their Integrated Risk Tool (IRT) for coronary artery disease, incorporating PRS alongside other risk factors, "*could help save more than 2,000 lives annually in the US alone*". This claim is based on their prediction that their IRT would 'upclassify' 7.02% of a pool of 105.2 million people (the total number of people aged 40 to 75 in the USA without cardiovascular disease), making 6.4 million more people eligible for statins. They calculate that 2,423 deaths would be preventable annually if 100% of these extra people took statins (or 1,551 deaths, if uptake and compliance with statin medication was 64%).[148,149] Even if the claims regarding reclassification are correct, this assumption is completely unrealistic: in the USA, uptake of statins varies in different groups, but is always lower in 'primary prevention' (i.e. groups who are not yet ill).[150] Adherence to statin therapy increased from 57.9% in 2007 to 63.8% in 2014 among patients initiating treatment following a heart attack, and from 34.9% to 37.6% among those with diabetes but without CHD, but remained almost constant between 2007 (35.7%) and 2014 (36.8%) for those without CHD or diabetes. Thus, a claim of 872 deaths

prevented annually in the USA would be more plausible (based on compliance of 36%), but this still assumes 100% uptake of the screening test, which is also highly unlikely (in the UK National Health Service, free cardiovascular screening has an uptake of about 50%[151], this would cut the estimate of prevented deaths again, to 436). Further, the uncertainties in the classification (meaning we cannot be confident that the right people are in the high-risk category) and the lack of evidence of improved health outcomes also needs to be borne in mind. What does being classified as at high genetic risk really mean, if there is no confidence that individuals have been correctly classified, as described above? How would people react to being given different PRSs from different companies, with contradictory results? Is using a PRS really cost-effective and are there better, simpler alternatives? Would some people classified as at lower genetic risk perhaps believe that they can continue to smoke or eat unhealthily, worsening health outcomes in that group? In short, prediction of health benefits is not the same as demonstrating this, in the real world.

There are significant inequalities in diagnosis and treatment of cardiovascular disease.[152] Because cardiovascular diseases are so common, even small changes in some risk factors could save a lot of lives. For example, health behaviours (smoking, physical activity, diet, and weight) and health factors (cholesterol, blood pressure, and glucose control) all contribute to cardiovascular health.[153]

The UK population is about 20% of the US population, so a prediction of 436 lives saved by adding a PRS into screening for cardiovascular disease in the USA would very roughly translate to 87 lives saved in the UK. Even if this prediction were reliable, it is a small number in comparison to what could be achieved through improvements public health measures or improvements to health services. For example, one study has estimated that 5.2 million cases of cardiovascular diseases could be prevented over 25 years in the UK if everyone was treated according to existing guidelines (although, of course, 100% detection and treatment is not possible in reality).[154] Another study of the UK National Health Service (NHS)'s existing cardiovascular disease screening programme (without added genetic risk scores) has argued, using computer modelling, that more lives would be saved by a combination of population-wide intervention (measures to reduce salt and sugar in processed foods and drinks, subsidised fruit and vegetables, and reducing smoking) and more targeted screening (including people only in the most deprived 40% of the population).[155] In this study 9,000 deaths are prevented, compared to 3,000 deaths from universal screening, whilst also reducing health inequalities. Although this study also relies on modelling, it suggests that alternative approaches which incorporate public health measures could easily prove more cost-effective than adding a PRS into an existing screening programme.

Guidelines regarding who should take statins vary significantly around the world. Whilst the evidence for secondary prevention (e.g. after a heart attack) is not disputed, there are disagreements about how many healthy people with risk factors but no symptoms should be given medication (known as 'primary prevention'): this reflects different individual and societal preferences (e.g. for altered diets rather than medicine), as well as uncertainties and variations in expected costs, side effects and benefits.[156,157,158] Whilst some researchers are concerned about side effects and the low absolute risk reduction in individual patients, others argue that everybody over 55 should take statins and other risk-reducing medicines, on the basis that this could save millions of lives without the cost of screening tests. [159,160] Age is the dominant risk factor in determining risk of CVD: adding further risk factors does little to improve screening performance, and neither does more accurate CVD risk estimation.[161,162] Even for secondary prevention (in people who already have CVD), adherence to medications such as statins and to lifestyle advice is low.[163,164] In this context, it is not clear that making small changes to existing screening tests, by adding PRSs (which also add to costs), is the best way to improve health outcomes.

A 2018 study found that incorporating a genetic risk score based on 27 SNPs into a conventional risk score was not a cost-effective approach for targeting statins for low- to intermediate-risk patients (assuming the test costs $100).[165] This is because testing carries additional costs without large gains in discrimination between patients.[166] A subsequent cost-effectiveness analysis by companies involved in PRSs (Allelica, Pacific Biosciences and Illumina), using a different PRS from that developed by Genomics PLC, claims that about 29 coronary artery disease (CAD) events (such as heart attacks) and strokes would be averted in 10,000 people over a 5-year period, or 50 over ten years.[167] In this model, only individuals with 'borderline' 10-year risk of CAD (calculated without the PRS) are given the PRS (these are people with 5% to 20% calculated risk). In the population studied, 16 002 people were classified as the primary prevention population (PPP) with 5890 having borderline or intermediate 10-year risk of CVD (calculated without the PRS). In this group of people, nearly 17% (987 people) with borderline or intermediate 10-year risk were in the top 20% of the PRS, and 652 people (11.07%) were not taking statins and therefore classified as high-risk based on the PRS but not under the current risk assessment without the PRS. The study concludes that including the PRS with other risk factors (as part of an IRS) is cost-effective when the genetic test is targeted at the subset of patients who fall into the studied group, i.e., 40-year-olds with borderline calculated risks, based on traditional risk factors. The first thing to note about this study is that it does not attempt to justify rolling out this PRS to the whole population (indeed, it shows that this would not be cost-effective). This is consistent with other studies, which have also found that targeted use of PRS would be much more efficient than blanket population-wide use and also with a public statement by the CEO of Allelica that "*It's important to carefully identify and focus on narrow intended populations where greater benefits are observed through PRS testing*".[168,169,170] Secondly, the results depend on the correct people being reclassified and the validity of the Net Reclassification Index (NRI), both of which may be questionable (as described above). Thirdly, the results are based on computer modelling, which often over-estimates the benefits of testing compared to the real world where things are always much more complicated (for example, a recommendation to base the dose of the blood-thinning drug warfarin on genetic test results was not supported by later clinical trials, which found the test did not improve health outcomes[171,172]). Fourthly, the model (which has been developed by companies trying to influence US health insurers to pay for their commercial product) contains some additional assumptions which might bias the results. For example, it assumes that 50% of the additional people identified by the PRS would take statins (higher than the 36% discussed above). Finally, the model does not consider alternatives to using the PRS (such as seeking to increase statin compliance in existing high-risk groups, providing alternatives for those who prefer not to take medication, addressing health inequalities, or introducing new public health measures).

The poor reproducibility of PRSs in populations not classed as of 'European ancestry' is a major issue discussed further in Sections 7 and 8. One study has attempted to assess the transferability of a PRS for coronary artery disease to British Pakistani and Bangladeshi individuals.[173] Although this paper advocates the use of PRS as part of an IRS, it in fact shows no significant increase in the C-index compared to calculating risk with the non-genetic risk factors alone. In addition, the relative accuracy of the PRS in the target population was only 42% (compared to its use in a population classed as European). The use of the Net Reclassification Index (NRI) as a measure of performance is questionable when there is no confidence that individuals are correctly classified (as described above), and this measure may be biased. In this study, 97.4% of participants were in the lowest 40% of the Index of Multiple Deprivation in the UK, but no attempt was made to consider the effects of deprivation on their health. The same research group also produced an IRS for type 2 diabetes in this population. Again, only small changes to the C-index were observed.[174] A more recent study in a sample of almost 80,000 US veterans (23.4% classed as non-Hispanic Black, 8.6% as Hispanic and 68% as non-Hispanic White), investigated whether PRSs for coronary artery disease and acute ischemic stroke predicted incident

atherosclerotic cardiovascular disease (ASCVD) events, including heart attacks, strokes and deaths.[175] In this study, the addition of the PRS to the traditional risk factor model increased the C index for all ASCVD outcomes by roughly 0.01 among participants classified as Hispanic or White and by 0.004 for stroke and all non-death outcomes among participants classified as Black. The Net Reclassification Index was also modest in all groups, with slightly better performance in women and at younger ages (but with smaller sample sizes for these groups).

Blood pressure is another area of research, with a recent study in the UK Biobank suggesting that a blood pressure PRS should be combined with blood pressure measurements and other risk factors (sex, age, race, ethnicity, body mass index, total cholesterol, high-density lipoprotein cholesterol, diabetes, cigarette smoking, physical activity, Townsend deprivation Index, statin use, and number of hypertensive medication classes) to help identify individuals at high risk of cardiovascular disease (CVD).[176] However, the paper reports a tiny increase in the C-statistic (AUC) from 0.728 to of 0.729 when the PRS is added to the risk prediction model, in people with normal blood pressure. There were also very small improvements in predictive value in people with untreated hypertension (an increase from 0.683 to 0.684 when the PRS is added) and people with treated hypertension (from 0.640 to 0.641). In this study, 59.7% of the population were identified as having untreated hypertension, based on measuring their blood pressure, suggesting that tackling this problem, whether through medication or improving diets, should be more of a priority than trying to refine individual risk predictions.

In one study of type 2 diabetes, a clinical risk score (CRS), based on established non-genetic risk factors, had a C-statistic of 0.839, compared to 0.709 for a PRS, 0.762 for a model based on 12 nongenetic exposures (referred to as a polygenic exposure score, PXS), 0.844 if the PRS was added to the CRS, 0.85 if the PXS were added to the CRS, and 0.855 if both the PRS and PXS were added to the CRS.[177] Thus, adding the PRS only modestly improved the predictive power compared to clinical risk factors, and the PRS was less predictive than a model based on environmental exposures (such as diet, alcohol and tobacco use).

Some studies have also investigated the use of IRS for predicting cancers. For example, one recent study has included a PRS based on 313 SNPs in a computer model to try to predict breast cancer in the second breast of women who already had breast cancer on one breast (this is known as contralateral breast cancer).[178] The computer model is developed from an earlier one which already included the effects of rare mutations in the BRCA1/2 genes and other factors such as age and the characteristics of the cancer in the first breast. As well as adding information from the PRS, this updated computer model also adds rare mutations in another gene (CHEK2), body mass index (BMI) and parity (the number of times a woman has given birth). Since both breasts have usually had the same exposures to environmental factors, as well as the same genes, predicting contralateral breast cancer should be relatively easy, but the AUC at 10 years was only 0.65, a slight increase on the earlier computer model (without the PRS) which had an AUC of 0.63. A further breast cancer study adds a PRS based on 313 SNPs to other risk factors, including a panel of mutations in rare genes (such as BRCA1/2 and others), to predict risk of breast cancer in a group women aged 46 to 73 years.[179] The computer model containing the PRS and the gene panel has an AUC of 0.672 (compared to an AUC of 0.536 for the risk assessment without any genetic risk factors), and thus its predictive value in the general population is still poor. This study excludes women who do not identify as White European (including Ashkenazi Jewish women), on the grounds that the PRS will not work well for them (see Sections 7 and 8).

5.6 PRSs combined with cancer screening

Some advocates of PRSs argue that, where the predictive value is too low for use as stand-alone screening tests, they could nevertheless be used as part of targeted screening programmes, particularly for cancers. The idea is to offer the conventional screening programme (for example, mammography for breast cancer) preferentially to a group calculated to be at higher genetic risk.[180] The reasoning is that cancer screening programmes are known to cause harm through overdiagnosis and overtreatment.[181] Selecting a smaller group of high-risk patients to screen would reduce the number of cancers identified by the screening programme, but could potentially also cut costs and reduce the harms caused by wrongly identifying cancers that don't exist or don't need to be treated. However, other scientists disagree and warn that the cost and complexity of adding PRSs into cancer screening programmes could also reduce the number of people that participate.[182] This might happen, for example, due to concerns about privacy, corporate control, lack of regulation, or racism (see Sections 8, 9, 10 and 11). In addition, the PRS itself is a form of screening, which could lead to people seeking treatment for being categorised as at 'high genetic risk', and higher caseloads for medical professionals without clinical benefit.[183] PRSs could worsen health outcomes if people take 'low risk' scores as a reason to disengage from screening altogether.[184] In reality, if PRSs were to be used in this way, people would have to be informed of their individual risk scores, and considerable confusion could then occur about their limited predictive value, as discussed above. In addition, expensive additional new screening tests might need to be introduced, such as magnetic resonance imaging for prostate cancer, and the potential for overdiagnosis and overtreatment would remain (since many men die with, but not from, prostate cancer, and PRSs do not improve risk prediction for aggressive prostate cancers with the potential to be fatal).[185,186] A 2022 review of whether PRSs would be a cost-effective addition to cancer screening (for prostate, breast or colorectal cancer) concludes that this is unclear, due to the absence of robust evidence on the costs of polygenic risk stratification, the effects of differential 'ancestry', potential downstream economic consequences, and unanswered questions about how large volumes of polygenic risk data would be collected and used.[187] A subsequent study reports that a PRS does not improve risk prediction of aggressive prostate cancer compared to a clinical risk predictor tool, and thus will not enhance clinical decision-making.[188,189] A 2023 study of the potential benefits of introducing PRSs for common cancers (breast, colorectal and prostate) similarly finds that the potential benefits of combining PRSs with cancer screening programmes are limited, even under favourable assumptions.[190] The authors highlight that this is because many or most cancers will occur in low-risk groups and because PRSs do not address the many flaws of cancer-screening tools, including over-diagnosis and limited reductions in mortality. This study also notes that, for rare cancers, the absolute numbers of cancer in the PRS-defined high-risk quantiles remain too modest for screening to be plausible.

Another UK study of breast cancer found that adding a PRS and additional lifestyle/ reproductive risk factors into an existing model (called BOADICEA, based on family history and rare breast cancer mutations such as those in the BRCA1/2 genes), led to only a small improvement in the AUC from 0.691 to 0.697.[191] This paper also reports an over-estimation of risk by a similar US model (known as the Tyrer-Cuzick, or IBIS, model), which the authors suggest may be due to not accounting for the correlation between the PRS and the contribution of family history that is already included in the model. Australian company Genetic Technologies reports an AUC of 0.636 for 5-year risk and 0.647 for lifetime risk for an alternative model called BRISK, which incorporates mammographic density and clinical risk factors with a PRS.[192] According to this paper, a third to a fifth of all women aged 40 to 70 years would need increased surveillance, and potentially risk-reducing medication (with side effects), if this model were implemented in clinical practice. Similarly, Genetic Technologies reports that a PRS for colorectal cancer only marginally improves a simple family history model (increasing the AUC from 0.666 to 0.673), and a combined PRS and

clinical risk model can only achieve an AUC of 0.663.[193] Modelling studies such as these are unable to demonstrate improved health outcomes, and the reported AUCs are well below those that would normally be considered acceptable for population screening. Further, they have generally been developed only for populations classed as of 'European ancestry' and are likely to have poorer predictive values in other population groups (see Section 7 and Section 8). US company Ambry Genetics has reportedly removed their polygenic score product from the market because polygenic scores 'have not been validated for use in patients of diverse backgrounds'.[194] In contrast, Myriad Genetics are marketing a multi-ancestry breast cancer PRS, based on categorising people as a percentage of three 'genetic ancestries' (issues regarding this methodology are discussed further in Sections 7 and 8).[195] Myriad's published paper reports an odds ratio of 2 for people in the top 10% genetic risk, which suggests a poor predictive value (low AUC) although the AUC is not reported.[196]

6. How important are genetic differences in determining the risk of common diseases?

"*It is tempting to imagine that there will be a transformative improvement in the predictive ability of polygenic scores through the discovery of more genetic risk variants. But modelling shows that, even in the theoretical scenario that all common genetic risk variants are identified and used in a polygenic score, they will still be limited in their ability to differentiate between those who will and will not develop disease*". Medical researchers writing in the British Medical Journal, 2023.[197]

"*Larger GWASs than those already done will improve PRS predictions modestly; predictiveness is inherently constrained by the low heritability of most common late-onset cancers*". Medical researchers in London and Oxford, UK [198]

Will more research improve the predictive value of PRSs and change the situation? This partly depends on how important genetic differences are (or are not) in a person's risk of developing one of these common, late-onset diseases, and partly on how complicated the relationship is between genes, biology, environment and chance, and the risk of developing a particular disease. These issues are considered further below.

Heritability is a measure of how well differences in people's genes account for differences in their characteristics, including their risk of developing a particular disease.

If a measured trait, such as height, in a population is plotted against the number of people who have a particular value of that trait), it usually shows the shape of a 'bell curve' (known as a 'normal' or 'Gaussian' distribution), with most people in the middle of the curve (e.g., at close to average height) and small numbers in the tails (very short or tall). The spread of the bell curve is measured by its 'standard deviation', or by its 'variance', which is the standard deviation squared. The heritability is the calculated proportion of the variance that can be explained by genetic factors (assumptions and criticisms of heritability are discussed in Section 7).

Traits such as height are known as 'continuous traits', because they are characteristics that change gradually over a range of values. But whether someone gets a disease or not is a 'discontinuous' or 'binary' trait (a person either has the disease or not) and the risk of getting that disease cannot be directly measured. For disease risks, the liability threshold model is used to explain how a large number of environmental and genetic factors may result in a disease. This model assumes that the observed disease status (i.e., whether or not a person develops the disease) can be described by a continuous unobserved liability, which captures all genetic and environmental risk factors that influence the disease risk. The disease is

assumed to occur when the subject's liability exceeds a certain threshold. For a disease, the heritability is the proportion of the variance in the liability to disease which can be accounted for by genetic factors. But the liability itself cannot be measured.

Heritability is not a fixed property of a disease or trait but depends on the population studied, including its environment. [199,200] Its scientific meaning is not the same as the common understanding that it measures whether or not something is inherited.[201] However, it is a potentially useful measure to help understand whether genetic tests could in theory help to identify a subset of the population who are at high genetic risk (the people in the 'high risk' tail of the bell curve). If the heritability of a given disease in a given population is zero, then a genetic test is no help at all – everybody is at the same genetic risk. In general, if heritability is high (in a given population), a PRS might be developed that has high predictive value, but if heritability is low, the predictive value of a PRS is always likely to be low – in other words, it will be a poor way to decide who is likely to develop the disease and who is not.[202]

Heritability is discussed further in Section 7, including concerns that it may be oversimplified and overestimated, but for now we assume existing calculations of heritability are correct and ask what these values mean for the likely predictive value of PRS. Traditionally, heritability was usually calculated using twins but today 'SNP heritability' is often calculated as part of the Genome Wide Association Studies (GWAS) used to develop PRSs.[203] For a given disease, the 'SNP heritability' is usually much lower than the heritability calculated using twin studies. This could be because some genetic variance is not captured by the DNA chip, and/or because twin studies may over-estimate heritability (this is discussed further in Section 7). Nevertheless, the 'SNP heritability' is the heritability that could in theory be explained by all the SNPs captured by a particular DNA chip (or 'SNP chip'). This includes all the SNPs that are directly measured by the chip, plus any that are inherited alongside those that are directly measured (this is known as 'linkage disequilibrium' and is discussed further in Section 8). The SNP heritability provides an upper limit to the predictive value of a PRS because it includes the effect of any SNP that could theoretically be included in the PRS (even if the link between the SNP and the disease has not yet been discovered).

First, it is important to be aware that many conditions have low heritability and therefore PRSs for these conditions would always be expected to have poor predictive value, however much research is done. Two examples of diseases with low heritability are lung cancer and the risk of being infected with, hospitalised with, or becoming critically ill with, severe Covid-19, as described below.

A 1995 twin study failed to find a significant heritability for lung cancer, but was largely ignored due to the on-going promotion of the idea that a genetic test would identify which smokers would develop this disease, which became a key part of the justification for the Human Genome Project.[204,205,206] A much larger calculation in 2000 (combining the results of multiple twin studies in Scandinavia) also failed to find any significant heritability.
More recently, a study in UK Biobank has calculated a SNP heritability for lung cancer of 8.3% (reaching 10% in 'ever' smokers and 3% in 'never' smokers).[207] This low heritability means that genetic tests aiming to predict who will get lung cancer in the general population will inevitably be low. These results are important because they highlight that, although only a minority of smokers get lung cancer, this does not automatically mean that a genetic test (or a PRS) can predict who would develop this disease. In reality even a perfect PRS for lung cancer would have very low predictive value (an AUC close to 0.5). In this case the risk is explained largely by environmental factors (exposure to cigarette smoke or other pollutants) and by chance (only about one in ten smokers develop the disease, perhaps because there are random processes involved in how much damage is caused to their lungs or how well the damage is repaired).

Similarly, for Covid-19, in a large study (called a meta-analysis) of results 60 studies in 25 countries, including more than 2.6 million people, the SNP heritability of being infected with, hospitalised with, or becoming critically ill with severe COVID-19 was calculated to be only 0.13%.[208] This tiny heritability means using a PRS for COVID-19 infection, hospitalisation, or risk of severe disease is no better than random guessing. Yet, several tests which claim to calculate genetic susceptibility to COVID-19 are already on the market. A study of direct-to-consumer (DTC) tests claiming to identify genetic susceptibility to COVID-19 concluded that they provide inconsistent results and are not based on established scientific information.[209] Although this conference presentation has not been peer reviewed, its conclusions are not surprising as a low heritability (close to zero in this case) inevitably implies a low AUC (close to 0.5), and hence very poor predictive value. Similarly, genetic factors do not provide an explanation for why some ethnic groups are at higher risk than others. An analysis of global data on COVID-19 clinical outcomes examining inequalities between people from minoritised ethnic groups, compared to the ethnic majority group, found that increased risks for some ethnic groups were largely due to inequalities which increase exposure risk and vulnerabilities to severe disease, including structural racism and racial discrimination.[210] These issues are discussed further in Section 8.

However, many other conditions appear to have higher heritability, so it's possible that PRSs for other diseases might be worth considering. For example, an overview (meta-analysis) of twin studies published in 2015 found an average (median) heritability for studied traits and diseases of nearly 50%.[211] This finding suggests that fairly predictive PRSs might be achievable for some diseases (a heritability of 50% implies an AUC of more than 0.85, which is better than many existing medical tests[212]). Twin studies are often cited in scientific papers as providing evidence that developing PRSs will be worthwhile (whether twin studies are reliable is discussed further in Section 7).

On the other hand, 'SNP heritability' calculations have tended to be much lower. As described above, the SNP heritability provides an upper limit to the predictive value of a PRS because it includes the effect of any SNP that could theoretically be included in the PRS (even if the link between the SNP and the disease has not yet been discovered). For example, SNP heritabilities for a wide range of diseases and traits have been calculated for UK Biobank by the Neale lab, and are available in a public database.[213] Apart from height (at 48.5%), the calculated SNP heritabilities are generally much lower than 50%. Even for height, a PRS published in 2021 performs no better than mid-parental height as a predictor of adult height in children.[214] For conditions with lower SNP heritabilities, prediction is expected to be poorer. For example, in these calculations, the reported SNP heritability of a major coronary heart disease event is 0.144 (i.e., 14.4%); diagnosis of chronic ischaemic heart disease is 0.164; diagnosis of cancer in the breast is 0.0218; diagnosis of prostate cancer (malignant neoplasm of prostate) is 0.105; and type 2 diabetes is 0.14. The highest of these examples (chronic heart disease at 0.164 or 16.4%) is equivalent to an AUC of 0.7, which is lower than most medical tests in use today.[215] Heritability depends on the population studied and, in studies to date, SNP heritabilities calculated elsewhere (e.g. Qatar, Korea and Uganda) have tended to be even lower than in Europe.[216,217,218] Estimates of SNP heritability for some conditions (such as schizophrenia and Alzheimer's Disease) in the UK Biobank database are too uncertain to be reliable, due to the relatively small number of cases in this study (despite its large size). In other studies, the SNP heritability for Alzheimer's Disease has been calculated as between 13% and 33% (compared to 58% from twin studies), the SNP heritability of schizophrenia has been calculated to be 24% (compared to 60% to 80% from twin studies) and the SNP heritability of major depressive disorder has been calculated to be 16% (compared to 30% to 40% from twin studies).[219,220,221] Estimates of SNP heritability for other psychiatric diseases are lower. For autism, a SNP heritability estimate of 0.13 compares to heritability estimated from family pedigrees of 0.8 (as with twin studies, assumptions are discussed in Section 7).[222] For

neurodevelopmental disorders a SNP-based heritability of 0.19 has been calculated (family-based heritability, 0.66).[223]

Now that GWAS have been conducted on large numbers of human diseases, it has become apparent that SNP heritabilities are generally low. For example, a combined statistical study (meta-analysis) using 23 biobanks, representing 2.2 million individuals, calculated SNP heritabilities (on the liability scale) for 14 conditions: the highest is only 10.73% (for gout).[224] The conditions included in the study were asthma, chronic obstructive pulmonary disease, heart failure, stroke, gout, venous thromboembolism, primary open-angle glaucoma, abdominal aortic aneurysm, idiopathic pulmonary fibrosis, thyroid cancer, hypertrophic cardiomyopathy, uterine cancer (in females only), acute appendicitis and appendectomy.

In 2008, the idea that calculating an individual's genetic risk of common diseases would be useful for their health was widely regarded as having failed. This is because the results from GWAS found only a small part of the heritability expected from twin studies.[225] This meant that the genetic variants that had been found had poor predictive value and were not useful to decide who was likely to develop a particular disease. For common diseases, the genetic component of the risk that had been identified was found to be very small: the rest was called the 'missing heritability'. When this paper was published in 2008, scientists were divided about whether this meant that heritability had been overestimated (see Section 7), or whether the missing heritability was yet to be discovered (or a combination of these two explanations). For example, some of the 'missing heritability' could be explained by many SNPs of such small effects that they needed bigger databases to be discovered, or by genetic differences (so-called Copy Number Variations) that are not measured by the DNA chips that are used in GWAS studies.[226]

Nearly ten years later, a 2017 analysis found that on average the variance explained by weighted Genetic Risk Scores (GRS) using common SNPs accounted for only 10.7% of the SNP heritability for 32 traits.[227] This has been increased subsequently by adding rarer SNPs found in larger studies: however, there is still a significant gap for most traits, and the SNP heritabilities are anyway much lower than the earlier calculations from twin studies, as described above. One 2019 study considered whether the 'missing heritability' is likely to ever be found, using data showing how more rarer SNPs associated with disease continue to be found as GWAS studies get larger.[228] This study looks at 16 traits which have been studied at least 3 times and for which at least 30 associated SNPs had been identified. It finds evidence that for 6 of the 16 traits the 'missing heritability' gap may never be closed, whereas for the other 10 traits this might be possible (although it still may not happen). Reasons why heritability from twin studies may be exaggerated are discussed in Section 7. A subsequent study by the same researchers reports similar results, but highlights that different methods may vary in the conclusions reached about a particular trait or disease.[229]

Advocates of PRSs often highlight how larger and larger studies have identified more SNPs of small effect and gradually explained a bit more of the 'missing heritability' (particularly for height), but they do not highlight how SNP heritability estimates for the majority of disease-related traits remain much lower than estimated from twin studies. This has important implications for the predictive value of PRSs. For example, a 2018 study reports that the majority of the SNP heritability of height in UK Biobank (estimated at 0.53 in this paper) can now be explained, achieving a correlation between actual and predicted height of about 0.6.[230] But this paper refers to "*numerous conditions with heritability on the 0.5 range, such as Alzheimer's, type I diabetes, obesity, ovarian cancer, schizophrenia, etc.*", for which effective predictors might be developed in the future, citing a link to heritabilities calculated from twin studies, rather than the much smaller SNP heritabilities now found. As noted above, the SNP heritabilities for these diseases are much lower (typically more like 0.1, i.e. 10%, than 0.5, or 50%).[231,232,233] This makes a massive difference to the potential predictive value of the PRS, raising questions about whether they can ever have sufficient predictive

power to be rolled out to the whole population. Whereas a SNP heritability of 50% suggests that an AUC of 0.85 could be achievable (if all genetic risk factors could be perfectly accounted for and included in the PRS), in reality a SNP heritability of 10% would imply a maximum achievable AUC of 0.66, which is too low to be useful.[234]

The SNP heritability provides an upper limit to the predictive value of a PRS because it includes the effect of any SNP that could theoretically be included in the PRS (even if the link between the SNP and the disease has not yet been discovered). In reality the predictive value of the PRS will fall short of this as long as the explained SNP-heritability (the part for which SNPs have been identified) is less than this. An example might have a SNP-heritability of 25%, only half of which has been explained: this would lead to only 57% correct placement on the top 20% of the risk distribution, and a prediction accuracy (the percentage of people correctly assigned to this risk category) estimated to be only 40%, leading to significant errors if the PRS were to be used in decision-making.[235] Even if 80% of the SNP-heritability were to be explained in this example, this study calculates that only 72.7% of individuals would be correctly classified as in the top 20% of genetic risk, as calculated by the PRS.

If SNP heritability is low, there is another important consequence because the high uncertainties for the genetic risk categories given to individuals using PRSs, as described in Section 5, reduce with sample size, but increase with the number of causal SNPs involved in the condition, and are highest for conditions with low heritability.[236] This means that risk predictions for complex diseases with low SNP heritability (and including a very large number of SNPs) are likely to remain highly uncertain and unreliable for individuals, as well as having low predictive value for the population.

In summary, "*Polygenic scores will always be limited in their ability to predict disease, as much of a person's disease risk is determined by factors that polygenic scores cannot measure*".[237]

It is important to remember that heritability can also vary from one population to another (see Section 7). Because 'heritability' varies with environment, this means the same disease can have different a heritability in a different country, and even in different populations within the same country.[238] This is because the separation of the causes of variation into genetic and environmental parts is a statistical calculation based on a fixed population in a fixed environment at a fixed time. This also means that a person's calculated 'genetic risk' and even their categorisation as at 'high genetic risk' is not fixed but may change with time due to changes in their environment.[239] Further consequences of the assumptions made when calculating the 'heritability' of a disease are discussed in Section 7.

7. Can we trust the algorithms?

The above discussion assumes that the computer algorithms used to calculate PRSs are basically correct in the common assumptions that are made. However, there are many uncertainties in these computer models and researchers make numerous simplifications and assumptions regarding issues that are not fully understood. For example, a recent paper lists sixteen "*major open problems*" in the understanding of the genetics of complex human traits.[240] Different methods are used by different researchers to create different PRSs, and these can give very different risk predictions for the same individual (as discussed in Section 5).[241] However, in addition, common simplifications and assumptions could also mean that all the algorithms differ from reality in important ways that might bias the results. Below, we first consider uncertainties due to imperfect measurements and data, then sources of bias, and then more fundamental doubts about whether the methods used make the right assumptions.

As noted above, PRSs are made using data from so-called 'genotyping chips' (also called DNA chips, microarrays or SNP chips, pronounced 'snip chips'). These chips measure the presence or absence of a particular chemical letter in a person's DNA (called a SNP) at a particular location in the genome. SNP chips are not always accurate: a recent study found that SNP chips are extremely poor for correctly genotyping very rare variants compared with sequencing data (which looks at the whole genome) and that, for an individual person, a positive result for a very rare pathogenic variant is more likely to be wrong than right. This has major implications for some genetic tests currently on sale direct-to-consumer (DTC).[242] For more common variants these so-called genotyping errors may be somewhat less important and other problems may be more important. In particular, SNP chips do not measure every chemical letter (a person's whole genome) because this is too expensive.

A typical SNP chip may measure millions of SNPs but a whole genome contains 3.2 billion chemical letters (or 6.4 billion if you count both pairs of chromosomes). In many cases, when a particular SNP is statistically associated with an increase in risk it is not because the measured SNP is having an effect, but because a SNP nearby on the genome is: the SNP that has an effect is known as a 'causal' SNP and is said to be 'tagged' by the SNP that is actually measured by the chip. Scientists use various methods to try to identify these missing causal SNPs, that are tagged but not directly measured. These methods always use the fact that the genome is inherited in chunks (called haplotypes) so that the same genes tend to remain near each other, and they often use Whole Genome Sequencing (WGS) from smaller studies to infer some of the missing SNPs (this is called imputation). Imputation is not exact and can only approximate whole genome sequencing (WGS).[243,244] Additional uncertainty remains in the PRS calculations due to the uncertainty as to which SNPs are causal, which cannot be proven purely by statistical association.

A further problem with all data is that current studies, although very large, are not large enough to accurately quantify the very many small effects on risk that are now being found: in other words, there is statistical 'noise' in the data which can mean real effects are not identified or spurious effects are found. Data is messy and biased and is always subject to multiple 'corrections' to try to obtain the right answers from the statistical methods that are applied to it.

There are inherent limits to the predictive power of PRSs due to the difficulty in separating the role of true causal SNPs from those that are linked to the disease or trait simply by chance. If the number of causal SNPs involved in a disease or trait is very large compared to the sample size, the causal and non-causal SNP cannot easily be separated and the PRS will have low predictive accuracy, even if the heritability is high.[245] Thus, if a very large number of SNPs are thought to influence a trait (known as the 'omnigenic' model), the idea of including millions of SNPs in a PRS requires ever-larger sample sizes, without necessarily achieving the required predictive value. If, on the other hand, a complex trait is influenced by multiple genes (known as the 'oligogenic' model), where the number of causal SNPs is small compared to the sample size, a PRS developed using only those SNPs which meet a threshold of statistical significance will perform better than one that includes more SNPs.[246]

Often, the statistical association between a particular SNP and a disease is confirmed in more than one study, but the size of the effect varies between different studies. The choice of how to weight the importance of the different SNPs can bias the results: for example, the same SNPs have a bigger effect on risk in a large European GWAS of type 2 diabetes than they do in a similar study by the US company 23andMe.[247] Results from multiple studies can be combined (for example, by the Global Biobank Meta-analysis Initiative, GBMI[248]), but different size effects may also reflect real differences between populations, leading to incorrect risk predictions if a PRS developed in one population is applied in another (as discussed further below).

A more fundamental problem is that the statistical link between a gene and a disease can be spurious if there are 'confounders', i.e., other factors that could be part of the true cause of the disease but which happen to be more common in people with particular genetic variants.[249] In this context, a major issue is the treatment of 'population stratification' in all GWAS studies. This issue, and other sources of confounding, are discussed further below.

The uncertainties considered above are not the only ones. PRSs also depend on a whole series of assumptions about how genes and environments contribute to human diseases and characteristics (known as traits).[250,251] These issues are also discussed below.

7.1 Problems with applying PRSs in different populations

In this section, we discuss the implications of genetic, social and environmental differences between different populations for the results of PRSs. One aspect of this is the use of corrections for genetic structure within populations, to try to avoid spurious associations between genes and disease. A related problem is that PRSs usually have lower predictive value in different populations: for example, a score developed in a database of people defined as of 'European ancestry' will typically work considerably less well in populations categorised as being of 'African ancestry'.[252] This means a person in one group can be wrongly classified as at 'high' or 'low' genetic risk, based on a PRS developed in another group (typically, this is in persons classed as of 'European Ancestry'). This has major implications, discussed below, and provides a fundamental reason to object to the use of PRSs in health services. The implications of the methods used to correct for population structure are discussed below. However, it is important to be aware that the idea of 'genetic ancestry' is, in itself, a simplification that is controversial. Because the methods used to calculate 'multi-ancestry' PRSs inevitably involve corrections for 'genetic ancestry', and since these categories are chosen in arbitrary ways, this can lead to people being categorised in ways that they may disagree with, and which are associated with a long history of racism, including slavery and genocide. These issues are discussed further in Section 8.

In statistics, a confounder is something, other than the factor being studied, that could be causing the results seen in a study. Confounders cause problems in all types of study (not just genetic ones), but in genetic studies the existence of confounders can mean that an increase in risk of a disease, for example, is wrongly attributed to a genetic factor, when it is really caused by a social or environmental one. If such a genetic factor is included in a PRS it can bias the score (leading to someone being wrongly categorised as at 'high genetic risk', for example) and also bias the estimation of 'SNP heritability' (making genetic differences seem more important than they really are in determining the risk of a particular disease).

In GWAS, major sources of confounding arise because genes and environments can be correlated in important ways. Confounding can occur for different reasons (genetic or environmental). Environmental confounding occurs when environmental and genetic factors vary in a correlated way across different regions or subpopulations (e.g., because a group in which particular genetic variants are more common also share similar diets). Genetic confounding occurs when genetic differences that do not cause a trait are correlated with other genetic factors that do.[253] Three major sources of confounding are discussed below: (i) population stratification (ii) familial confounding (due to the influences of family members on each other); and (iii) geographic confounding (due to regional differences in socio-economic factors). [254]

'Population stratification' is well-recognised problem with genetic studies, including the GWAS studies used to calculate PRSs. Population stratification occurs when a given

population is more likely to have a disease but also more likely to have certain genetic variants which are not linked to the disease. Statistical methods which compare one population to another will usually conclude that these genetic variants are linked to the disease, simply because they are more common in the population that gets the disease more often, even if they have nothing to do with the cause of the disease. This type of spurious association between genetic factors in disease (or other traits, such as height) has led to some major errors in the past.[255]

In short, PRSs, and estimates of variance explained by genotypes (i.e. of 'SNP heritability'), can be biased upward in the presence of confounding with population structure.[256] Often, PRSs are reported only for people of 'European ancestry', with other groups (who are minorities in most studies) omitted from the calculations. This is a major problem because such PRSs may misclassify the genetic risks of people categorised as of different ancestries. In addition, even PRSs developed using only data from people classed as of 'European ancestry' may suffer from confounding due to hidden population structure within this group. Because this is a well-known problem, various corrections are now made for population stratification in the calculations of GWAS statistics and of PRSs, to try to eliminate this problem. However, these corrections also introduce uncertainties, have not eliminated the problem, and can create new problems due to the assumptions that are made, as discussed below.

The usual method used to correct for population structure is called 'principal-component analysis' (PCA).[257,258] This is a method for reducing the complexity of data by allocating it into several categories (the principal components) that explain the largest fraction of variability in the data. Assigning genetically similar samples to different groups for analysis reduces stratification by limiting the degree of population structure remaining in the sample. As noted above, many PRSs are constructed by omitting data from people who are not classed as of 'European ancestry'. PCA is then used to correct for population structure within the 'European Ancestry' group. However, some GWAS may involve multiple different ancestries.[259] In multi-ancestry studies, samples are either assigned to 'genetic ancestry groups' and each group studied separately, or the whole data set is analysed together, using methods to try to control for population structure. 'Genetic ancestry' really means 'genetic similarity' of particular continental groups (for example, groups defined as 'European', 'Asian', 'African' or 'Native American'). Consumer genetics companies calculate what they call a person's 'genetic ancestry' by defining particular 'source populations' from which all people alive today are assumed to have descended. These categories are inevitably somewhat arbitrary (based, for example, on naming ancestry categories which are similar to present-day populations) and involve choices and assumptions.[260] In this method, 'source populations' are not necessarily explicitly defined but can be constructed implicitly by the algorithm.[261] Alternatively, broad categories can be chosen, such as the 'African', 'East Asian' and 'European' reference groups used by Myriad Genetics in a paper on its breast cancer PRS.[262] In theory, categorising people into different ancestry groups reduces the problem of 'population stratification' within each of these groups, but it does not eliminate it entirely, and it also often leads to individuals who don't fit well into the groups being dropped from the analysis.[263] The 'genetic ancestry' assigned to each individual may also differ from their self-reported ancestry, particularly for those classed as non-European.[264] Even if more diverse groups are studied in the future, individuals of mixed ancestry might need to be excluded if there are insufficient numbers for the statistical analysis. Although the 'genetic ancestry' groups are based on the clustering that the researchers see when they analyse the data, the choice of where to draw the boundaries between groups is essentially arbitrary. This is because human populations are not distinct.[265,266]

Unfortunately, choices made when making corrections for population structure have major impacts on polygenic risk scores in all studies.[267] This means that PRSs for complex diseases depend critically on the methods used to construct the scores. This is a major

source of unreliability. Even for the relatively simple example of height, PRSs vary significantly between studies and this can lead to seriously erroneous conclusions.[268,269,270] This problem is considered so serious by some authors that they regard PCA as "*unsuitable for population genetic investigations*", due to findings that the method can generate "*erroneous, contradictory, and absurd results*" and recommend re-evaluating all PCA-based studies.[271]

As noted in Section 5, even within Europe, the performance of PRSs drop significantly when applied to different European populations.[272] This may reflect different environmental or genetic backgrounds or more fundamental problems with the assumptions which mean that PRSs are poorly reproducible (discussed further below). This is in addition to the problem that most PRSs to date have been developed in populations categorised as of 'European ancestry', which are not representative of global populations.

A 2019 study of GWAS research found that, in total, 71.8% of participants are recruited from only three countries; the US, UK (with the most study participants), and Iceland (with the highest proportion of its population on a DNA database, run by the commercial company DeCode).[273] There is much evidence that PRSs derived in a particular population give erroneous results if applied to people in different populations, particularly in groups described as of 'African ancestry'.[274,275,276,277,278,279,280,281] Recently, there have been numerous calls to expand research studies to include greater diversity: this includes calls to recruit more study participants from minority ethnic groups in the UK and USA and plans to expand biobanks in other countries, particularly in Africa. However, to understand whether this is a good idea or not we need to understand why PRSs are not replicated well in different populations, and whether calculating PRSs for people of 'African ancestry' is really a good priority for health (this is discussed further in Section 8).

The advocates of PRSs tend to focus on genetic explanations for why PRSs do not work well when they are applied in different countries, because these could in theory be addressed by doing larger studies with more diverse populations and more detailed measurements, such as whole genome sequencing (WGS). One important issue is that GWAS rely on the fact that parts of the genome are inherited together in chunks (known as 'linkage disequilibrium'), so that the SNPs on the chip are inherited together with other causal SNPs. Because these chunks are different in populations with different ancestries, the relationship between the SNPs that are measured directly by the DNA chip and those that cause disease may be different in different populations.[282] Populations with different 'genetic ancestry' may also have different causal SNPs. Bias arises because most genetic variants causally linked with a disease are rare and population specific, and common variants linked with a particular disease are also often much more common in the study population than elsewhere.[283] One study has found that PRSs inferred from European GWASs are biased by genetic drift in other populations even when choosing the same causal variants, and that biases in any direction are possible and unpredictable. [284] Genetic drift is the change in frequency of an existing genetic variant in the population due to random chance: it can cause particular genetic variants to become rarer or more common in a given population, and even disappear.

Whilst these are major problems, and must be taken seriously, differences can also arise due to differences in environment.[285] In particular, "*Non-genetic factors, such as environmental exposures may be correlated with ancestry due to a shared local environment (familial or community effects) or the relationship between ancestry and sociocultural factors such as race and ethnicity*".[286] Recent simulations suggest that for common variants, differences in effect sizes have a bigger effect on limiting the predictability of diseases such as type 2 diabetes and rheumatoid arthritis in different populations, than the frequency of the variants.[287] This could be partly due to the effects of unmeasured rare variants which are correlated with the measured SNPs, but it could also be due to gene-gene or gene-

environment interactions (discussed further in the next subsection) or due to changes in effect sizes due to different exposures in different populations. For example, a genetic variant that is associated with skin cancer will have more effect where people are more exposed to radiation from the sun, and this can be influenced by social factors (such as whether people use sun cream and sun hats), as well as by geography. Thus, cultural variation is also part of environmental variation and may have larger effects on human adaption.[288,289,290] Different populations, and different social and ethnic groups within a given country, will have different environmental exposures, diets and social and economic circumstances. For example, in the UK, type 2 diabetes risk is higher in people classed as South Asian or African Caribbean, compared with those classed as European, but reduces in second-generation compared to first-generation immigrants, and is strongly influenced by obesity and socio-economic status.[291] As a result of varying environments and socio-economic circumstances, risks associated with small genetic differences will be enhanced, reduced, or even disappear under different environmental conditions, and new ones will appear.[292, 293] In a recent example, environmental factors appear to modify which genetic variants effect lipid levels in Uganda, compared to other countries.[294] Due to this complexity, simply doing more genetic studies will not resolve the problem of the lack of transferability of PRSs between different populations (see also Section 8).

Poor reproducibility of PRSs between different European populations has also been observed.[295] As well as genetic differences, confounding of environmental and genetic effects is possible, including of social effects.[296,297] Although genetic risk scores derived from people classed as of African ancestry tend to perform better in sub-Saharan Africa than scores derived from people classed as European, there is poor transferability between different populations within Africa.[298] This is not surprising when considering the diversity of populations within Africa (cultural, linguistic, phenotypic and genetic).[299] If the effect sizes of genetic variants depend not only on ancestry but also on environment, the transferability of genetic scores from one population to another will be limited.[300]

'Downward causation' is a term used to describe social forces acting on (selecting and sorting) individuals based on phenotypes (a person's observable characteristics, such as skin colour or height).[301] This creates artificial genetic associations. For example, if people with red hair were excluded from school, poor educational attainment would be associated with genetic variants contributing to red hair, although the cause of the lack of education would be the social policy. GWAS and PRSs can therefore capture artificial genetic signals, which may be particularly important in the context of racism (see Section 8).

Confounding is one type of bias, 'collider bias' is another. This occurs when there is a third (unknown) factor (the 'collider') influencing the outcome of the study.[302] This could be another factor leading to bias in GWAS and PRSs, particularly when genes and environment are correlated and when there is selection bias in the study (i.e., the people in the study are not representative of the general population).[303,304]

Unlike population stratification, familial confounding and geographic confounding have only recently begun to be discussed in the context of GWAS.[305]

It is well known that both social and environmental effects can cluster in families.[306] The effects of this clustering on health or education can be wrongly attributed to shared genetic factors, when social privilege or a family preference for healthy diets is really what is being passed on to the next generation. Nevertheless, familial confounding is a relatively new area of study for geneticists. Some researchers argue that the parents' genes (or genes of other family members) have indirect effects on a child via the rearing or social environment of the family. [307,308] An example is the idea that parents with certain genes might feed their children more. These genes would then be statistically associated with the child being overweight, even if they had no direct effect on the child's weight. However, other

researchers object to the idea of 'indirect genetic effects', because there is no evidence of a causal effect of parents' genotypes on their children.[309] Familial confounding could also be due, not to indirect genetic effects, but to shared rearing environments such as social status, culture, worldviews, values and habits. If these are amplified over generations they are known as 'dynastic effects'. Such gene-environment correlations can inflate estimates of genetic influences, especially for complex social traits where the transmission of social advantages such as status and wealth are significant.[310] Like population stratification, familial confounding will also bias genetic effect estimates in GWAS. Genetic studies, including GWAS, also generally assume 'random mating', whereas in reality 'assortive mating' occurs in human populations: for example, couples often have similar levels of educational attainment, height, or socio-economic class. Assortive mating is another source of bias which can exaggerate the estimated SNP heritability of a disease or trait.[311,312] Evidence that many SNPs affect multiple different human characteristics or diseases (known as 'pleiotropy'[313]) may also be influenced by indirect genetic effects, although the extent of this remains unclear.[314,315] PRSs for many apparently unrelated diseases appear to be correlated, however a recent study suggests that these findings are biased, and that the apparent correlations may be caused by the effects of assortive mating.[316]

Geographic confounding occurs due to regional differences in socio-economic or environmental factors.[317] It can involve active processes such as selective migration or 'brain drain' (particular types of people leaving an area), or passive processes such as government policies affecting particular socio-economic groups (that may share certain genes). As with familial confounding, this can mean that certain genetic variants are associated with poor health outcomes, even though those genetic variants are not causing the disease. Geographic confounding has been shown to exist, although its importance is unclear.[318] This type of confounding is likely most important for traits related to socio-economic status, such as educational attainment, but may also be important for overall health. Participation bias (the tendency of studies such as UK Biobank to include more people who are wealthier and in better health than the general population, for example), can also distort genetic associations (increasing or decreasing the effect size of a SNP, and changing SNP heritability estimates).[319]

7.2 Conceptual issues: do PRS algorithms make the right assumptions?

Section 6 highlighted the low values of 'SNP heritability' estimated for common diseases and explained how the 'SNP heritability' places an upper limit on the proportion of the variance that can be explained by SNPs using a DNA chip, and hence on the predictive value of a PRS. Section 6 also highlighted the gap between the estimated 'SNP heritability' of a trait or disease and its heritability calculated using studies of twins. Although 'SNP heritability' and heritability from twin studies can be compared directly for continuous traits (such as height and BMI), care should be taken because they do not measure exactly the same thing.[320] For diseases, the situation is even more complicated because of the assumptions that are made about the underlying liability to disease.[321] Nevertheless, as described in Section 6, high heritabilities from twin studies are often used to justify the development of PRSs. In this subsection we discuss whether the apparent gap is due missing variants that have yet to be discovered, or whether there are fundamental problems and biases in the way that heritability is calculated using data from twin studies. These potential problems relate to the complexity of complex traits and hence the assumptions made when PRSs are calculated. Thus, in some cases they raise doubts about the reliability of the algorithms and whether undertaking larger or more detailed studies, or more studies in different populations, can ever improve the predictive value of genetic risk predictions. In reality, both explanations could play a role and the gap referred to as the 'missing heritability' could be partly closed in future without necessarily improving PRS predictions or their transferability from one population to another.[322]

Classical methods of estimating heritability from twins or relatives (known as 'top down' approaches) are based on the idea that traits that are more highly correlated among relatives are more heritable.[323] On average siblings share half their genome by descent from their parents. Thus, there is a direct relationship between the correlation of a trait like height between siblings and its heritability, provided some assumptions are made. These assumptions relate to the relationship between the extent to which the genotype is shared and the extent to which the trait is shared (using a model developed by the eugenicist Ronald Fisher in 2018, discussed further below[324]). Because siblings may also share environments (to an unknown extent), it is not possible to be sure that shared traits are due to shared genes, rather than shared environments. Therefore, twin studies are often used, based on the 'equal environments' assumption that identical twins (monozygotic twins, born from a single egg) and non-identical twins (dizygotic twins) share their environment to the same extent. Twin studies rely on many assumptions that can lead to over-estimates of heritability. Only one of these is the 'equal environments' assumption.[325] Others include assumptions about a lack of statistical interactions between genes (epistasis), or between genes and environment, and a lack of assortive mating (the tendency of people to marry people of a similar height and level of educational attainment, for example). It is now widely recognised that early estimates from twin studies were biased and gave results that were too high, although there is little agreement on the extent of the bias, or its main causes.[326, 327] Possible explanations are discussed in more detail below.

Methods of calculating SNP heritability from GWAS are based on the same underlying idea but use observed genotype data to estimate heritability from the relatedness of individuals and the correlation of their measured traits, in a given study population.[328] There are many different methods of calculating SNP heritability that may give rise to different estimates.[329] A study of common measured traits (such as height, BMI and educational attainment) in 86 billion pairs of individuals has concluded that the SNP heritability tends to underestimate the pedigree-estimated heritability, due to incomplete linkage disequilibrium in distant relatives (meaning that rare SNPs are imperfectly tagged by the DNA chip). [330] However, this study also finds "*further evidence for the systematic inflation of heritability estimates from classic twin studies*", which it attributes largely to the effects of assortive mating. Nevertheless, this study has not completely resolved the debate regarding the extent and causes of the bias in twin study results.

For many traits and diseases there is still a large gap between the 'top down' heritability estimated using twin and family studies and the 'bottom up' SNP heritability. Some scientists argue that there is no reason to question the validity of the methods used to calculate PRSs (using the weighted sums of risk alleles), as: the risk distributions are what Fisher predicted for a large number of variants with weak effects, there seems to be no evidence for strong gene–gene interaction (discussed further below), and the PRSs that have been developed generally work (to the extent described above) in external validation samples.[331] In this view, the gap between the 'top down' heritability and the SNP heritability is likely to be explained by other types of variants that are not captured by GWAS, including rare non-coding variants and tandem repeat variants (a sequence of two or more DNA bases that is repeated numerous times).[332] This idea is discussed further below.

However, other scientists believe that there is something fundamentally wrong with the methods used to calculate heritability and the associated genetic risks, including polygenic risk scores (PRSs). One major underlying issue is that calculations of heritability assume that the distribution of a characteristic such as height in a given population can be split into genetic and environmental components, when in reality each depends on the other and interact in many complex ways.[333,334] Additional uncertainty is introduced by the idea that there is a hidden liability to a disease, which manifests itself only when a threshold is exceeded, because the calculated heritability depends on the assumptions made about

something that does not exist and hence is not observable.[335] Heritability calculations also make unsubstantiated assumptions about how the risk of each genetic variant combines to create the total risk of disease: this is based on the so-called 'additive' genetic model, invented by the eugenicist Ronald Fisher in 1918.[336] The additive model is used when calculating 'SNP heritability' but it is also relevant to how heritability is calculated using twins. In these calculations, the additive contribution is assumed to dominate, with smaller interactive terms allowed to explain only the residual part of the variance. For traits (such as height) the additive model is used directly, but for diseases, it is important to be aware that the additive model is used on the liability scale (due to the assumption made regarding a hidden liability to disease) and this means it is multiplicative on the risk scale (although it is sometimes still referred to as the 'additive' model). [337]

Estimates of heritability from twin and family studies are highly variable between studies and some of this is due to poor study design, including questionable assumptions that bias twin study results upwards (such as assuming there is no shared environment).[338] Other assumptions are embedded in all twin and family studies. All current methods of calculating heritability continue to assume the genetic risks of each SNP combine in a way described by Fisher's 'additive' model, which implies that there are limited gene-gene or gene-environment interactions or correlations between genetic and environmental factors (these are only introduced as secondary effects to explain data that does not fit the additive model). The way that the genetic components of the variance are split into additive and other more complex components, inevitably leads to the conclusion that there is a large additive component (and hence that interactions are unimportant).[339] However, in reality, a given genetic variant does not appear to carry a fixed risk but has effects dependent on the context (other genes, the rest of biology, and the environment). Unsurprisingly, Fisher's model (devised by a eugenicist in 1918, before the famous 'double-helix structure of DNA was even discovered), is difficult to reconcile with much that is now known about evolutionary biology. One opinion piece notes that, "*The current models are stretched to their limits and require substantial adjustments to explain and deal with the observations*", but also observes "*strong resistance to change in this field*".[340]

In essence, estimating heritability from twin data involves fitting the data to Fisher's model, but the assumptions made in doing so lead to a calculation of the maximum possible role of genetic differences in any given disease or trait, and provide, not a true value of the heritability, but an upper limit to it.[341,342] In other words, data from twins alone does not provide enough information to calculate heritability without making additional assumptions, which tend to bias the results upwards.[343] If any of the assumptions made are wrong, genetic differences will be less important than expected and the potential predictive value of measuring them will be reduced. In addition, the results could be more difficult, and perhaps impossible, to calculate.

Recent research suggests that the non-additive component of the variance is small (meaning it adds little to the SNP heritability).[344] However, this does not mean that it is unimportant. Non-additivity may be widespread throughout the genome, but much larger studies may be needed to detect it (this paper estimates such studies would need to include 7.5 million samples). The authors consider only dominance variance (nonlinear interaction effects between alleles at the same place, or locus, on the genome), but epistasis (interactions between alleles at different loci) may also be important. Importantly, non-additive effects can create 'phantom heritability', i.e., lead to the over-estimation of heritability in twin and family studies.[345] Some researchers argue that epistasis has major implications for personal genetics.[346] One view is that epistasis may in fact dominate the variance in many situations, leading to inflated estimates of heritability: this is expected due to the effects of natural selection which removes the additive genetic component of the variance over time.[347,348] Underlying this is the idea that evolution has developed robust systems by evolving redundant gene networks that are resistant to fluctuations, both genetic

and environmental.[349] However, different definitions of epistasis have been used by different scientists, and in general the importance of epistasis in limiting the predictability of common diseases, is unknown.[350] Gene-environment interplay (consisting of both interactions and correlations between genes and environment) may also play a role.[351,352] Some evidence of genome-environment interactions has been published in some studies: a recent study of depression is an example.[353] Interpretating these findings and their implications is not straightforward and account must also be taken of the assumptions regarding a hidden liability to disease, which in practice means the standard model is multiplicative on the disease risk scale. [354] However, in general, if interactions are more important than has been assumed, the 'top down' estimates of heritabilities that are made today (e.g. from twin studies) will be overestimates.[355,356,357,358,359] And, importantly, obtaining more sequencing data may not improve the accuracy of PRS predictions.[360]

Another view, which attempts to reconcile those who support the 'additive' model with those who argue that reality is more complex, is that "core" genes (for which the gene product has a direct effect on the trait or disease) explain a small proportion of the heritability in a relatively simple way, whereas "peripheral" genes (which affect the disease or trait indirectly through a network of interactions) explain a larger part, and gene-environment interactions provide another layer of complexity.[361] This 'omnigenic' model can potentially be extended by considering both 'core' and 'peripheral' environmental effects. In this model, the effects of 'core' genetic variants would be largely consistent across populations, but the effects of 'peripheral' genes would not be (due to differences in the structure and complexity of the peripheral gene network, the nature and extent of environmental interactions, and the genetic architecture of the trait). In this model, genetic variance would appear additive within a population, but the effect sizes of many variants would change in different populations. Since such variants make up most of the heritability, the majority of variants would have different effect sizes in different populations (as has been observed) and PRSs developed in one population would not generally transfer well to another, and would differ across time.[362]

Random ('stochastic') variation is also minimised when Fisher's model is fitted to twin data, or treated as a part of the environmental variance, yet it likely plays a major part in the diseases people get and their characteristics and behaviours.[363] For example, as described above, the risk of contralateral breast cancer is poorly predicted by PRSs and other known risk factors, even though a woman's breasts will in general have the same environmental exposures throughout life, as well as the same genes.[364] Similarly, a recent study found the frequency of cancer arising in the contralateral kidney after cancer in the first kidney was only 1.2%.[365] This is not surprising, as many environmental exposures that cause cancer involve random processes.[366] In addition, even identical twins reared in the same environment inevitably vary in their characteristics, and a study in mice that had been inbred (so they were nearly genetically identical), in controlled environments, found that most of the variance (70 to 80%) in body weight could not directly explained by either genes or environment.[367] An alternative explanation for this finding is the existence of non-linear (chaotic) developmental processes.[368,369]

Above, we have discussed concerns that heritabilities from twin studies may be over-estimated. Alternatively, could SNP heritabilities be significantly underestimated, suggesting that PRS predictions could be significantly improved, perhaps by including more detailed genetic variantion from whole genome sequencing (WGS), rather than from SNPs?

The 'heritability gap' (or part of it) might occur because SNPs do not capture all the genetic variation between individuals. For example, for schizophrenia, the 'top down' heritability is estimated at 60–80% and the SNP heritability in studies to date is around 24%.[370] Copy number variants (CNVs) occur where a particular section of DNA is repeated a different number of times in different people. Finding CNVs involved in the risk of some diseases might explain some 'missing heritability', however CNVs are rare and therefore likely to

account for only a small proportion of heritability.[371,372,373] Whereas a SNP changes a single chemical letter (nucleotide) in the DNA sequence, an indel incorporates or removes one or more nucleotides, and some SNVs which disrupt gene function may occur too rarely to be picked up in a GWAS. However, in schizophrenia, rare gene-disruptive rare SNVs, indels, and Copy Number Variants (CNVs) appear to account for less than 10% of the variance.

Estimates of 'SNP heritability' do not rely on the 'equal environments' assumption. However, other problems can still affect these estimates. Different assumptions made when SNP heritabilities are calculated lead to different answers.[374] Other issues include the existence of confounders such as hidden 'population stratification', familial confounding and geographic confounding, all of which can lead to heritability being over-estimated.[375,376,377,378,379,380]

For example, one recent study estimates SNP heritabilities using a large group of 178,086 siblings.[381] This can provide less biased estimates because the 'within-sibship' SNP heritability calculations are unlikely to be affected by 'familial confounding'. In this study, the within-sibship SNP heritability for educational attainment was only 4% (compared to 13% from the general population), and for height was 34% (compared to 41% in the general population). This is consistent with other findings that the predictive values of PRSs are reduced in siblings compared to non-sibling pairs, with particularly large reductions for educational attainment.[382] It suggests that at least some estimates of SNP heritability have been biased upwards, particularly for social traits. In the higher estimates, some of the SNPs could be tagging shared geography, class, affluence and culture, rather than SNPs that directly affect a person's supposed inherent capacity to study.

On the other hand, SNP heritability estimates can be underestimates due to imperfect tagging of SNPs by the DNA chip.[383] Thus, it is possible that the calculated SNP heritability might be increased if whole genome sequences are used instead of SNP chips, as all the possible genetic differences between individuals can then be included. However, the evidence for this (discussed below) is, so far, not particularly encouraging.

One study published to date (which is not yet peer reviewed) uses Whole Genome Sequences (WGS) to estimate the heritability of height and Body Mass Index (BMI). This should find any missing heritability due to genetic variants that are not captured by DNA chips. This study states in the discussion that "*Our estimates largely but not fully recover the heritability estimated from pedigree data*". However, this is not really the case for BMI: after correction for population stratification (discussed in Section 7), the study estimates a heritability of 0.6 (60%) for height and 0.23 (23%) for BMI.[384] In UK Biobank, the SNP heritability calculated for height is 0.485 and for BMI is 0.249.[385,386] Thus, using whole genome sequences has slightly increased the calculated heritability for height (compared to that calculated using SNPs) but not increased it at all for BMI. Elsewhere in the paper, these authors note that the pedigree estimate (based on relatives or twins) for the heritability of height is 0.7 to 0.8 (which they describe as close, although it remains higher than their calculation), but for BMI is 0.4 to 0.6, which is much larger than the study could find in the measured genome sequences. A large study has reported a heritability estimate of 0.66 for height from siblings, after accounting for assortive mating (which biases results from close relatives upwards to 0.82 in this paper).[387] This paper finds that heritability estimates for BMI are not biased by assertive mating and reports a SNP heritability of 0.239, an estimate from close relative pairs of 0.497, and an estimate from full-sibling pairs of 0.807. Thus, the WGS results have not closed the 'heritability gap' for BMI, but returned a result rather similar to the SNP heritability.

A study using WGS in animals (three different breeds of bulls) found that WGS did not explain any more of the variance in stature than SNP panels containing 50,000 SNPs.[388] In addition, the use of a more limited set of 133 SNPs with potential causal effect gave better predictions across breeds than using larger numbers. In humans, a more recent study has

attempted to quantify whether rare whole-genome sequencing variants might explain the 'missing heritability' by looking at their contribution to the variance in the levels of 414 difference proteins in human blood (plasma proteins).[389] It finds that these rare variants identified using WGS may be important in calculating an individual's risk, but they add little to the existing SNP heritabilities (accounting for 8.5% of the heritability at most, depending on the method and population studied). This is because the variants that have the most effect are extremely rare.

A more recent study of 22 common traits and diseases in UK Biobank includes only coding variants (the part of the genome known as the 'exome').[390] It finds that rare coding variants explain only 1.3% of the variance on average (much less than common variants) and that rare coding variants will contribute only modestly to 'missing heritability'. These findings are supported by a subsequent paper led by scientists from the US company Illumina (see Section 9).[391] Looking at 78 phenotypes, including both medical diagnoses and laboratory tests (such as cholesterol levels) in exomes from 454,712 UK Biobank participants, this study reports that the average phenotypic variance explained was 10.1% for a common-variant PRS, 0.4% for a rare variant PRS and 10.4% when using a combination of the two methods. Although this industry-led study claims that combining rare variants (which have relatively large effects) into a unified genetic risk model results in "*greatly improving the clinical utility of genetic-based risk prediction*", this claim is based solely on the increased power to detect individuals in the very 'high risk' tails of the distribution (above the 99% percentile). It does not address the issue that low heritability will limit the predictive value of the combined PRS, as measured by the AUC, even if rare variants are included (see Section 5 and Section 6). Thus, the addition of rare coding variants will not significantly improve the utility of the PRS as a screening test, or render it any more meaningful for the vast majority of individuals in a population. Although this study argues for increasing sample sizes in biobanks, because the number of rare variants identified increases linearly with sample size, the effect sizes of rare variants discovered in larger samples will be smaller, limiting the additional contribution to the explained variance. These two studies do not quantify the effects of rare non-coding variants (i.e., the parts of the genome outside the 'exome'), which could explain more of the 'missing heritability'.[392] However, other research suggests that coding variants explain a much larger fraction of the heritability for low-frequency variants than for common variants (due to negative selection) and this suggests that rare and ultra-rare non-coding variants would also explain little of the heritability and would also not explain the 'missing heritability'.[393]

Thus, the evidence suggests that the performance of PRSs as screening tools in the general population will not be much improved by the inclusion of rarer genetic variants, if these could be identified using exome or whole genome sequencing.

Some of the issues discussed in this subsection are related to disagreements about the 'conceptual model' (in this case Fisher's model) which is used to analyse the data. In science, conceptual models change as evidence accumulates that the old model cannot explain. An example is the Ptolemaic model in which the planets move around the sun on circular orbits, compared to more recent models in which the planets (including the earth) all move round the sun. It is important to understand that even the Ptolemaic model has some predictive value, especially if additional circles (called epicycles) are added to the orbits to obtain a better fit to observations of how the planets move across the sky. In many fields of science, it is recognised that uncertainty caused by the wrong conceptual model is much greater than uncertainty due to noisy data, i.e., changing the conceptual model can make a much bigger difference to predictions. However, in the development of PRSs, alternative models are commonly dismissed, leading to the risk of 'confirmation bias' (the tendency to interpret information in a way which confirms one's own views).[394] The problem for researchers is that, if Fisher's model is wrong (overly simplistic) and/or GWAS and PRSs are inevitably confounded by environmental influences, it becomes impossible to split to

variance of a trait into separate genetic and environmental components, and the whole idea of calculating PRSs could then fall apart.

Correcting this problem likely requires properly accounting for complexity.[395,396] This is because decisions to use models that do not incorporate complex interactions are based primarily on hypotheses of convenience and not on plausible biological phenomena that are inherently complex.[397] Although it is statistically convenient to treat the genome as a kind of 'genetic code' in which each SNP has a fixed effect on the risk of a disease, this is not how biological systems actually work. Developments in this area will likely depend on developing a better understanding of metabolic pathways and how the biology underlying such pathways results in complex interactions, within and between cells and the environment.[398,399,400,401,402] However, although such work might improve understanding, it is important to note that it is not expected to improve the predictive value of PRSs.

The above issues are important for several reasons. Firstly, low SNP heritability puts an upper limit on the predictive value of PRSs, as described in Section 6, but the 'bottom down' calculations of higher heritabilities (e.g., from twin studies) have led some to believe that this might be improved by using larger studies and perhaps whole genome sequencing (WGS). However, if these heritabilities have been exaggerated there is little scope for developing future methods that have much higher predictive value. This is because any calculation of genetic risk will inevitably have poor predictive value if (measurable) genetic differences are not particularly important in determining which people will develop a disease. Secondly, lower heritability means higher uncertainty in an individual's polygenic risk score, even if the 'additive' model is correct, so that a given individual cannot be confident that they have been correctly informed whether they are at high genetic risk or not.[403] Already, the predictive value of PRSs are low (Section 5) and the complexity of issues such as accounting for hidden population structure and bias in datasets cast major doubts about the reliability of PRSs (Section 7). Thirdly, the transferability of PRSs from one population to another may not be solvable by further studies if the effect sizes of most SNPs vary from one population to another (particularly if they depend not only on the genetics of the population but also the environment).[404] If the 'additive' model is (even partly) wrong and the real relationship between genes and disease is much more complex, involving many interactions, individual risk predictions could become completely meaningless and impossible to calculate. In fact, some scientists have long-argued that the predictive value of small genetic differences will be extremely limited.[405,406]

Hence, despite the claimed progress in identifying many rarer, smaller SNPs of small effect, using larger studies, the development of PRSs remains highly controversial. Many scientists remain to be convinced that PRSs are useful tools for health or that future research can improve their predictive value. Evidence suggests that, as old conceptual models are abandoned, 'top down' estimates of 'heritability' are likely to become smaller and more realistic, and the role of random variation, complexity and inevitable uncertainty will have to be acknowledged. Tests of low predictive value should not be rolled out as screening tests in whole populations, although they may have more limited applications in specific situations.[407]

8. Race, eugenics, societal impacts and global implications

"*In humans, race is a socially constructed designation, a misleading and harmful surrogate for population genetic differences, and has a long history of being incorrectly identified as the major genetic reason for phenotypic differences between groups. Rather, human genetic variation is the result of many forces— historical, social, biological—and no single variable fully represents this complexity…The structure of genetic variation results from repeated human population mixing and movements across time, yet the misconception that human beings can be naturally divided into biologically distinguishable races has been extremely*

resilient and has become embedded in scientific research, medical practice and technologies, and formal education." Committee on the Use of Race, Ethnicity, and Ancestry as Population Descriptors in Genomics Research, US National Academy of Sciences, 2023.[408]

"*Encouragement of the biomedical community to transition from race-based to race-conscious research is critical. Although hundreds of studies have demonstrated worse health outcomes for Black patients than other races, race is a social construct and not a causal variable or a surrogate for innate biology. Thus, while Black race may be associated with worse health outcomes on a population level, Black patients also are affected by structural racism and disparities in SDOH [Social Determinates of Health], regardless of their income class or educational level*." Medical researchers in the USA, 2022.[409]

In Section 7 above, we discussed why PRSs are usually not replicated well in different populations. But we glossed over what is meant by a population, and by people's 'genetic ancestry' and ethnicity. The discredited idea of 'race' and racism is based on the idea that some people are genetically superior or inferior to others.[410] The methods used to calculate PRSs involve corrections for 'genetic ancestry', and/or the removal of certain groups from the analysis, as described in Section 7 above. The use of 'genetic ancestry' has been criticised because it risks perpetuating old ideas of racial types in the creation of supposedly distinct categories that name people as Africans, Europeans, Asians and Native Americans, for example.[411,412] These categories are inevitably arbitrary and, furthermore, as discussed in Section 7 above, data belonging to people who don't fit neatly into these categories is often discarded in the process of developing PRSs. At the moment, most PRSs are based on data from people classed as of 'European ancestry'. When data from multiple populations or different ethnic groups is used, the use of such categories is largely hidden in the calculations, but this may not remain the case if PRSs are fed back to individuals. There is a danger that these categories reinforce racist beliefs (such as the idea that there are different 'breeds' of human, or that some groups of people are superior to others), even though this is not supported by the evidence.[413,414,415]

Who should use a 'White British' PRS or an 'African' or 'Asian' PRS? Will PRS calculations incorporate calculations of 'genetic ancestry', or use self-reported ethnicity in ways that people are not told about? For people who migrate from one country to another, should they use a PRS developed in their country of origin, or the country they have moved to (where their environmental exposures, socio-economic circumstances and habits may have changed, and where complex social effects may lead to changes in the younger generation[416])? What about people who do not fit easily into these simplistic categories?

Race and racism have biological consequences for racially defined groups.[417] Systematic racism is a more plausible explanation than any genetic explanation for the finding that African Americans suffer worse health outcomes than European Americans. There is no evidence that Africans have more unfavourable genetic variants than non-Africans.[418,419] In addition, race and ethnicity are often correlated with socio-economic status and other environmental risk factors for disease.[420] For example, one recent US study found lower state-average educational quality was more common among Black individuals and associated with higher dementia risk.[421] As described in Section 7, genetic studies tend to attribute effects that may be caused by social or environmental factors to genetic ones, thus distracting from social and environmental causes (including racism), as well as emphasising risk factors that cannot be modified, rather than ones that can. This leads to criticism that indigenous peoples, for example, are implicitly expected to give their DNA to further genomics projects as conceived by Europeans. Critics argue that such projects define indigenous peoples in a particular way, as genetically distinct peoples that white scientists have the right to control and study.[422]

A recent study reports multiple issues with the handling and interpretation of DNA data from Roma people (the largest minority group in Europe).[423] In many cases, samples have been collected from people and/or shared without adequate consent or any record of consent and deposited in public databases, including for law enforcement purposes. In others, participants seem to have given some kind of consent, but it is unclear whether they understood exactly how their DNA would be used. Genetic researchers use disrespectful, stigmatizing and pejorative terms such as 'Gypsies' or 'inbred', or refer to Roma people as a 'genetic high-risk group' in publications, and use questionable methodologies to draw conclusions about the Roma people as a whole. This problem is not limited to this minority. Similar issues led the Diné (Navajo people) in the USA to establish a moratorium on human genetic research studies.[424] In 2010, Havasupai tribal members in Arizona were awarded damages and repatriation of blood samples used for genetic research purposes outside the original consent.[425] Numerous indigenous peoples have had their DNA sampled in the past based on broad verbal consent and two journals have recently retracted six papers that use DNA from Chinese minority ethnic groups. Some researchers have highlighted the possibility that genetic research could risk the stigmatization or discrimination against ancestral groups in Africa (if these are defined based in their genetic similarity, as discussed in Section 7).[426] Mistrust has also been created in Africa by what is known as the 'Sanger incident', in which samples and data collected by academics in South Africa were allegedly used for the development of commercial gene chips (although this has been denied).[427]

The evidence of poor health outcomes in ethnic minority populations is often used to reinforce the idea of race, i.e., to interpret the differences as due to biology (specifically genetics), rather than environmental and socio-economic factors (including the effect of racism). In turn, this influences the questions researchers ask and the way they interpret their data, to reinforce a racialized view of human biology.[428] Examples of detrimental impacts include more than a decade of research which attempted to characterise the high incidence of type 2 diabetes in indigenous populations (particularly the Native American Pima people) as due to genetic differences (compared to white Americans), whilst ignoring the impact of a major shift from rural, healthy diets to dependency on unhealthy food aid.[429,430,431] A recent meta-analysis of prostate cancer studies found that Black men in the USA have similar or better prostate cancer outcomes when access to care is equal and social determinants of health are properly considered: yet, much research has focused on attempting to find biological (usually genetic) explanations for why prostate cancer outcomes are worse in Black patients in the general population.[432] From genetic researchers' point of view, attempts to expand sample collection to more diverse populations may be driven by a desire to improve statistical studies by capturing as wide a range of genetic variation as possible.[433] However, this is not the same as including historically disenfranchised groups in research that could improve their health, and, according to this study, "*it remains unclear whether and how procuring more samples of underrepresented genetic variation will mitigate health disparities for underrepresented groups*". If this type of research is a poor priority for improving the health of such populations, seeking to enrol them in genetic studies – as opposed to addressing inequalities or relevant socio-economic and environmental factors (see Section 5) - is the wrong approach.

Other problems are exemplified by a recent study of PRSs for psychiatric disorders (schizophrenia, bipolar disorder and depression) amongst US military veterans.[434] In this study, participants were classified as being of African or European ancestry using a method which combines information on genetic ancestry with self-identified race/ethnicity (SIRE), but which prioritises SIRE unless this information is missing, and recognises that SIRE acts as a surrogate to an array of social, cultural, behavioural, and environmental variables, many of which are correlated with trait variation or disease risk.[435] Nevertheless, in this study of psychiatric illness PRSs, the groups are referred to as of 'broadly European ancestry' and 'broadly African ancestry' throughout, implying that the differences between the groups are

essentially genetic. The study reports that the PRSs can identify high risk groups for schizophrenia and bipolar disorder amongst those it describes as of 'European ancestry', with smaller effects sizes in the group categorised as of 'African ancestry', but does not calculate any measures of predictive value (which is likely to be poor, see Section 5). Not highlighted in the abstract or the summary, but noted in the text, is the much higher absolute risk of schizophrenia and major depression amongst those described as being of 'African ancestry', and the fact that the study did not look at aspects of the veterans' military service which might explain the much higher rates of psychiatric disorders in veterans than the general population. The stark differences between the risk of schizophrenia and depression in veterans defined as of 'African ancestry' compared to those in the 'European ancestry' category is illustrated in another paper by the same group (which also continues to focus on the role of PRSs).[436] By focusing only on genetic explanations for risk, and using the term 'ancestry' to describe what are largely social categories, these studies, like many others, risk diverting attention away from potentially modifiable causes of poor mental health. This problem may be exacerbated when genetic studies are expanded into other countries, where historic, economic, and social contexts may be very different.[437]

This problem is reinforced by the ongoing use of the model developed by the eugenicist Ronald Fisher in 1918, as discussed in Section 7, to which the data from GWAS is usually fitted, and which always maximises the calculated role of genetic differences in explaining individual differences.

In Section 7 we discussed why many genetic researchers are calling for greater diversity in genetic studies. But would undertaking large GWAS studies in Africa, and calculating PRSs for people categorised as of 'African ancestry' really be good for people's health?

Firstly, this report has questioned whether PRSs are a good priority for health, even in rich countries (see Sections 5, 6 and 7 above). The 'individualised' approach, with its potential to undermine public health, is likely an even poorer priority in low- and middle-income countries, with more limited infrastructure and more pressing social and environmental problems. Secondly, there are reasons to believe that PRSs will have even poorer predictive value in countries with greater genetic diversity. Thirdly, issues of privacy (Section 11), stigma and discrimination may be exacerbated in some countries: for example, identifying non-paternity has more serious implications for women in countries where sex outside marriage is illegal, and in countries with poor human rights records there may be greater concerns about how political opponents (and their relatives) could be tracked using their DNA. Finally, who decides that PRSs should be a priority in Africa, for example? Currently, this is not a bottom-up decision but a top-down one, easily influenced by vested interests (see Section 9), and global power dynamics, rather than by the best priorities for health.[438] Even within wealthy countries, the general public, and particularly minoritized communities, may feel they don't have a lot of say over research priorities. For example, in the UK, the Nuffield Foundation on Bioethics asked a focus group at the West Bromwich African Caribbean Resource Centre about the future of ageing.[439] The group valued independence, strong social relationships and fundamental living requirements, such as warm housing, as important attributes to ageing well and some felt a lack of trust in technology, public bodies and commercial companies, especially when considering how their personal data might be used and stored. Throughout their discussion, there was reportedly a greater emphasis on community and fundamental needs being met than on new technology.

There are many potential broader social impacts of implementing PRS. For example, PRSs could be used to seek to predict educational attainment. This is despite the fact such scores suffer from the same limitations as those for complex diseases, including poor predictive value for individual pupils, low heritability, high risk of misclassification, and the likely existence of confounding factors.[440,441,442] A detailed analysis of research in the area of genetics, intelligence and behaviours (such as criminality) is beyond the scope of this report,

but many conclusions drawn from developing PRSs for complex social traits are likely to be misleading.[443] If PRSs are used widely in medicine, it is highly likely that PRSs will also be developed for such traits, potentially leading to controversial applications outside of medicine. There is a long history of attempts to use claims about genetic differences to advance unjust social policies.[444] In all such cases, there is a risk that policies and resources could ultimately be decided based on genetic categories, rather than on a person's own achievements or behaviour. This problem is exacerbated because GWAS and PRSs can wrongly attribute social causes to genetic differences (discussed as 'Downward causation' in Section 7).[445] For example, if people with darker skin have poorer access to good education, due to a legacy of racism, genetic variants associated with dark skin may appear to be associated with lower educational attainment, even though this association is not causal. This could exacerbate racism if it leads some to claim that people with darker skin are inherently incapable of high educational attainment. The same could apply to people from a lower social class.

This blurring of the boundaries between health and behavioural research is already happening. For example, some researchers have questioned the use of 'broad consent' for UK Biobank, because studies of the genetics of same-sex sexual behaviour have been conducted using the genetic information in this data set, although the consent given by participants refers only to "*health-related research purposes*".[446,447] Almost any behaviour can be interpreted as 'health related', rendering this kind of broad consent effectively meaningless. Similarly, a recent study of the genetics of educational attainment used data from the UK Biobank and 23andMe, amongst others, although it is at least debatable whether UK Biobank participants would regard this as a 'health-related research purpose' (23andMe uses an even broader consent to 'scientific research' for customers who opt-in to research). Data from the US 1000 Genomes Project were also used: participants who consented to this project were told it would help "*find genes and genetic variants related to health and disease*".[448] These examples highlight how little control people taking part in genetic research may have over the kind of studies that are done. Because UK Biobank does not feed back research results, no direct harm to participants occurred. However, in future projects, PRSs may be provided directly to participants and stored in medical records or even on people's mobile phones. Calculating PRSs for sexual behaviour could be particularly dangerous in countries where homosexuality is illegal (even though the predictive value of such PRSs would likely be very low).[449]

In the case of autism, a large-scale GWAS (Spectrum 10K, funded by the Wellcome Trust) has been paused due to ethical concerns raised by members of the group targeted by the research.[450] Such a step is unprecedented. One issue raised by some is the difference between the perspective of neuro-minorities, such as autistic people, that they are a normal part of human diversity (the 'neurodiversity paradigm'), and the view of biomedical and genetics researchers that autism is a disease or disorder that should be cured or eradicated. This is complicated by the spectrum of severity of the condition and the reality that some parents of children with severe autism may view the issues differently.[451] Some critics of the proposed research argue that as long as some traits and differences are stigmatized, developing PRSs for those traits paves the way for genetic selection and eugenics.[452] Other critics argue that it is not clear how the study will improve participants' well-being, and that its aim seems to be more about collecting DNA samples and data sharing than about the people who are expected to take part.[453] In 2018, 63 percent of autism research funding ($247 million) in the USA went to risk factors and biology, with just 9 percent ($36 million) of funding to services and lifespan issues, which are of more importance to autistic people and their families.[454] The Spectrum 10K study is currently undergoing a review, including a consultation process with autistic people and their families, before planning to re-start.[455,456]

A particularly controversial application of PRSs is in embryo selection. Although widely criticised on ethical and scientific grounds, PRSs are already being marketed in the USA to

parents using in vitro fertilisation (IVF).[457,458,459,460,461] If PRSs are provided to whole populations, it is likely that some people will wish to use the scores for embryo selection, even if they are not in reality useful for this purpose. This exacerbates concerns about stigma and discrimination being associated with being categorised as at 'high genetic risk'. Concerns also include the potential revival of eugenic policies of the past, under which 'undesirable' traits were supposed to be eliminated from the gene pool.[462]

Stigma and discrimination may take different forms. For example, there is potential for genetic discrimination in insurance and employment. A wide variety of (partial) safeguards have been adopted to limit or prevent genetic discrimination in different countries.[463] However, these are far from comprehensive, raising concerns that genetic risk predictions could lead to the refusal of insurance, higher premiums, or reduced employment prospects.

9. Commercial interests, power and control

"*An overwhelming sense of hype and a rush to translate dominates the field of genetic research of disease prediction using genetic risk scores (GRSs)*" (A group of nine medical researchers, 2020).[464]

The enthusiasm for PRSs can partly be explained by the role of vested interests.

In the early days of the Human Genome Project, the tobacco industry and the food industry were major players who invested in genetic research and promoted the idea of identifying individuals who are 'genetically susceptible' to common diseases such as cancer, hypertension and type 2 diabetes. Such companies wished to emphasise genetic causes for diseases such as cancer, rather than their own products, and to promote 'personalised' prevention strategies, rather than population-wide restrictions on the products that they sell.[465,466] In addition, the pharmaceutical industry became interested in the idea of treating the 'pre-symptomatic patient', which could lead to a significant expansion in the market for medicines.[467,468,469] This would expand the drug market for healthy, wealthy people, rather than poor people who are more likely to be sick. Today, pharmaceutical companies have several different motivations for investing in genetic research, including potential drug discovery, as discussed below. Most major public research funders no longer collaborate with the tobacco industry, and thus its role is now very limited. However, major players promoting the future use of PRSs today are companies supplying DNA testing services and equipment, and computing companies who will store and/or analyse the data. The scientists working in this field also have a major interest in obtaining funding for their work.

A major player in most genetic studies is the US company Illumina, which is a major supplier of DNA chips and of genetic sequencing technologies and is seeking to increase its revenue.[470,471] A rival US company, Thermo Fisher Scientific, is also a significant player in this market.[472]

For example, the contract for the DNA chip design and manufacture for the UK's 'Our Future Health' project (which aims to return PRSs to 5 million participants) has been awarded to Illumina Cambridge Ltd, whereas genotyping participants in UK Biobank originally used a DNA chip from Affymetrix (now part of Thermo Fisher Scientific).[473,474] Illumina is also one of the founding industry members of 'Our Future Health', as is Thermo Fisher.[475] As well as profiting from genetic research studies, these companies hope to convince investors that the future market for their products could include whole populations. The US company Allelica (see also Section 5) has offices in New York, London and Rome and is seeking to commercialise PRSs for multiple diseases.[476] Allelica and Illumina have a licensing arrangement that allows Illumina to offer Allelica's PRS software to its customers.[477] Illumina researchers recently proposed the idea of adding a 'rare variant' PRS (based on data from

exomes, rather than DNA chips) to a 'common variant' PRS (based on data from DNA chips), in order to seek to address some of the problems with PRSs discussed in this report.[478] This paper claims to have greatly improved the clinical utility of genetic risk prediction, yet, as discussed in Section 7, the combined PRS reported in it only very marginally improves the potential predictive value in the general population. The 'competing interests' section of this paper shows that the methods have been patented, providing an extra commercial incentive to promote them. Illumina is a partner of Genomics England to deliver whole genome sequencing in the NHS, and thus might expect to profit from a method that combines both DNA chip and sequencing technologies.[479]

Illumina has been particularly active in lobbying to seek to expand its market in the UK. In 2009, the then CEO of Illumina told the Times that by 2019 it would have become routine to map infants' genes when they are born, and that conditions such as diabetes and heart disease could be predicted and prevented.[480] These claims were made despite the fact that, at that time, attempts to predict such diseases from genetic information had been a total failure.[481] The claims were linked to plans by the then UK Government, led by Tony Blair, to share heath records and genetic data without consent, which were subsequently dropped.[482] A decade later, former Prime Minister David Cameron reportedly lobbied the then health secretary Matt Hancock to attend the September 2019 International Summit on Population Genomics alongside Illumina's then executive chair Jay Flatley, months before Illumina won a £123m contract with Genomics England (a company owned by the Department of Health and Social Care).[483] Cameron did not lobby on the Illumina contracts and was subsequently cleared of accusations of unregistered lobbying for Illumina.[484] However, he did promote the idea of expanding genomic sequencing. His spokesman stated, "*David Cameron's work for Illumina has never involved any discussion of commercial contracts. It has predominantly involved promoting the benefits of genomic sequencing and the world-leading example of Genomics England to other countries around the world. He has done this in Australia, the US, the Gulf, India and more recently in online calls with interested parties in Japan and Holland*".[485] Hancock was also directly involved in claiming that genetic predictions of common diseases would be good for health. The former Health Secretary was highly criticised by experts for claiming that a supposedly predictive genetic test for 18 diseases, developed by Genomics England, meant he was at high risk of prostate cancer and that it had led him to book a blood test on the NHS.[486,487] The Secretary of State was accused of showing an "*astonishing level of ignorance*" about the use of such tests.[488] Writing in the British Medical Journal, researchers note, "*the then UK health secretary Matt Hancock told the Royal Society that having a polygenic score for prostate cancer "may have saved my life" and he would ensure that he did not "miss any screening appointments in the future" after being told that he had a 15% risk of developing prostate cancer by age 75, neglecting to mention that the background population risk is 13% and that there is currently no screening programme for prostate cancer in the UK*".[489] This example illustrates how politicians may receive and promote a biased view of the potential benefits of PRSs, influenced by commercial interests. The lobby group Public Policy Projects is also funded by Illumina and other companies with an interest in genomics.[490] Its reports include 'Genomics Revolution', which states that "*Polygenic risk scores could be routinely used in primary care to identify those patients at highest risk from cardiovascular conditions and other disease*".[491]

In addition to the role of DNA testing companies, such as Illumina and ThermoFisher, other companies seek to profit from selling the interpretations of genetic data, either by selling PRSs Direct to Consumer (DTC) or to health services (or both), and/or by selling access to genetic data to other companies to do research.

In the USA, some PRSs are already being sold direct-to-consumer (DTC), largely via the internet. For example, the company 23andMe has one of the largest customer bases for DTC genetic tests, reportedly containing more than 2.5 million customers.[492] 23andMe began marketing a new (unregulated) polygenic risk score for type 2 diabetes in 2019,

although the numbers of 23andMe's customers that have been given the PRS are currently unclear. 23andMe uses a custom Illumina DNA chip.[493] Much larger numbers of customers have taken 23andMe's genetic ancestry tests, so their total test kit sales had reached 11 million in 2021 and 13 million in 2023.[494,495] 23andMe was acquired by Richard Branson's Virgin Group in a $3.5 billion deal in 2021, despite being a loss-making company (its net loss for 2023 is predicted to be from $325 million to $335 million).[496] Virgin Group's interest was reportedly due to the potential use of its customer data in drug discovery (via deals with large pharmaceutical companies).[497,498] Other companies developing or selling commercial PRSs (via clinicians, rather than directly to consumers) include Myriad Genetics (based in the USA) and Genetic Technologies (in Australia).[499,500] Genetic Technologies describes its PRS as a 'consumer-initiated' test, meaning that consumers order it but results are analysed a delivered by a physician.[501] US company Ambry Genetics has reportedly removed their polygenic score product from the market because polygenic scores 'have not been validated for use in patients of diverse backgrounds'.[502] Some small companies are attempting to market PRSs online: for example, Estonian company Antegenes is marketing PRSs for cancer in the UK, via a company called 'Everything Genetic Ltd'.[503,504] Antegenes is a spin-out company from the University of Tartu, which maintains the Estonian Biobank (containing the DNA of 200,000 individuals genotyped with an Illumina DNA chip).[505] Other companies that currently sell tests of single genes for clinical use are conducting research on PRSs and considering marketing such tests in future.

The pharmaceutical industry has a variety of different interests in GWAS, including but not limited to developing PRSs. Identifying new causal genetic variants involved in a disease can help understand the mechanisms of disease and potentially lead to identifying new drug targets, even if the predictive value of these variants is poor. However, this requires considerable additional research and the Human Genome Project has not led to the bonanza of new drug targets that was originally claimed.[506] As described in this report, developing PRSs is of significant commercial interest because they can potentially be used to expand the drug market to 'pre-symptomatic' patients (people categorised as at 'high genetic risk' of a disease). In addition, some researchers believe that PRSs could be used to speed up clinical trials, because results might be obtained faster by testing drugs only in those classified as at 'high genetic risk', although there are significant potential problems with this idea (including the need for participants to take a genetic test of little relevance to them, as discussed in this report).[507]

In 2021, there were 41 active national genomics projects around the world, studying human genomic variation, with a variety of aims (as well as developing PRSs, these can include identifying disease mechanisms and drug targets).[508] Many of these involve public-private partnerships, with public funding used to set up the biobanks (samples linked to genetic and medical data) and commercial companies (largely pharmaceutical companies) paying to gain access to the data for research. In addition, DNA testing companies, such as Illumina and Thermo Fisher, are involved, as well as companies providing services to store and analyse the data. The majority of GWAS publications have been funded by the United States' National Institutes of Health (NIH), with UK funders second (14% of grants acknowledged in GWAS publications, funded mainly by the Medical Research Council, the Wellcome Trust and Cancer Research UK).[509] The numbers of participants in GWAS (from 2007 to 2017) were led by the US, with nearly 11 million (41.01% of the total) and UK with 2.25 million (10.45% of the total), followed by China (7.96%), Japan (7.66%), South Korea (4.08%), Finland (3.47%), the Netherlands and Germany (2.79% each), Australia (1.75%) and Iceland (1.13%). GWAS can be used for purposes other than calculating PRSs (for example, as a step towards identifying the biological function of genes involved in a disease). However, the papers cited in this report highlight that developing PRSs is a major driver for this kind of study, particularly in the US and Europe, and there are significant commercial interests involved in this approach. Large studies calculating PRSs are also taking place in China[510] (with the same limitations as US and European studies[511]).

The Global Biobank Meta-analysis Initiative (GBMI) is a relatively new collaborative network of 24 biobanks including samples and data from more than 2.2 M individuals. The Uganda Genome Resource has recently been added to the network of 23 other biobanks (one from Australia, one from West Asia, four from East Asian countries, eight from European countries, and nine from North America).[512]

Numerous other genomic medicine initiatives exist worldwide, although many are at an early stage of development, and not all will lead to the development of PRSs.[513] Concern about the poor reproducibility of PRSs in non-European populations has led to a number of initiatives to expand data collection in other countries, for example, the Human Hereditary and Health in Africa consortium (H3Africa) is funded by the US National Institutes of Health (NIH) and the UK's Wellcome Trust.[514] However, as noted in Section 8, it is unclear whether the priorities of US and UK funders really align with the healthcare needs of the targeted populations. Other studies are looking into the possibility of sequencing the genome of every baby at birth, again with a focus on the US and UK: this is controversial but is not discussed further here, since the primary aim is diagnosis of genetic disorders, not the calculation of PRSs.[515] However, many of these projects propose storing genomes for life, so the feedback of PRSs could happen in the future.

The research projects discussed above are generally not currently feeding PRSs back to individuals, due to the uncertainties in their interpretation, and (in some cases) lack of consent to this from study participants. However, there are already some exceptions and some proposals to change this in the future. In Finland, 3,177 Finnish individuals in the P5 Study have been given estimates of genetic and absolute risk of future type 2 diabetes and coronary heart disease, based on PRSs and clinical risk factors, via an online portal.[516] In the USA, the eMERGE (electronic MEdical Records and GEnomics) network is a national network funded by the National Human Genome Research Institute (NHGRI).[517] The eMERGE network has selected 10 PRS for initial clinical implementation by returning results to 25,000 people, recruited to include a high proportion from ethnic minority groups.[518,519] In the UK, there are plans to provide PRSs to over 5 million people in the National Health Service (NHS), as part of a new partnership between the NHS and private companies, called "Our Future Health" (OFH) (formerly known as "Accelerating Detection of Disease").[520]

Participants in 'Our Future Health' (OFH) in the UK will be recruited via the NHS (including via its blood donation programme) but the storage and analysis of data will be undertaken by commercial companies: hence, this is essentially a commercial enterprise, fronted by the NHS and provided with some public subsidy. At its own mobile recruitment clinic, OFH offers free health checks as an incentive to sign up, as well as promising future feedback: "*At their clinic appointment, as well as having a blood sample and some physical measurements taken, volunteers will be offered information about their own health, including their blood pressure and cholesterol levels. In the future, volunteers will also be given the option to receive feedback about their risk of some diseases and have the opportunity to take part in cutting-edge research studies*".[521] In January 2022, OFH announced £100 million in investment from life sciences companies, which are leading its design and delivery.[522] OFH also received initial funding of £79 million from UK Research and Innovation (i.e., funding from the UK Government). Unlike many other genetic research projects, OFH plans to feed PRSs back to participants, using scores that would be based on SNP data from DNA chips. The project's protocol states (p.51) "*Our Future Health is committed to providing individual-level genomic results, in particular genomic risk scores, to participants who consent and wish to receive this type of information*".[523] This is despite most experts in a recent study stating that PRSs are not ready for clinical application.[524] On its website, OFH makes claims, such as, "*In the context of heart disease, Our Future Health's extensive database will allow researchers to drastically improve the tools doctors use to predict a patient's risk of heart disease – and even allow interventions to begin before the disease has started in a person's*

body" and "*The programme will be producing integrated risk scores which include information on genetic susceptibility which will show more accurately who is at higher risk of common diseases*".[525] Such claims are highly misleading in the context of the poor performance of PRSs, and the limited scope for significant improvement (as discussed in Sections 5 and 6).There are links between the OFH project and the UK company Genomics PLC (see Section 5), which is preparing to market PRSs commercially.[526] In October 2022, Our Future Health announced a partnership with Genomics PLC to generate polygenic risk scores (PRSs) for volunteers who join the study.[527] In March 2019, Genomics PLC put out a press release in which Professor Sir John Bell, Regius Professor of Medicine, University of Oxford, and leader of the UK Government's life sciences industrial strategy said: "*In December 2018 the government announced the Accelerating Detection of Disease programme as part of its life sciences sector deal to harness the use of artificial intelligence (AI) to support research, early diagnosis, prevention and treatment across the major diseases. The data released today by Genomics plc clearly demonstrates the potential of approaches such as the use of polygenic risk scores to help catch diseases early or even prevent them altogether*."[528] Professor John Bell (now Professor Sir John Bell) has argued for genetic risk predictions to be rolled out across the UK National Health Service (NHS) since 1998.[529] As well as being the Government advisor who first proposed the project, he is a director of the companies 'Our Future Health'[530], 'Our Future Health Trading Ltd'[531], Genomics England Ltd.[532], and of Oxford Science Enterprises PLC[533] (formerly Oxford Sciences Innovation, OSI), one of Genomics PLC's investors. Genomics PLC announced it had successfully completed a $30 million funding round in March 2021, with investors including Foresite Capital and F-Prime Capital, as well as existing backers Oxford Sciences Innovation and Lansdowne Partners.[534] As noted above, Illumina is also one of the founding industry members of 'Our Future Health', as is Thermo Fisher.[535] Eurofins Genomics will undertake the genotyping using a customised Illumina DNA chip.[536] Other founding industry members include pharmaceutical companies such as AstraZeneca, GlaxoSmithKline and Roche.[537] The medical testing firm Randox is also on this list.[538] By describing itself as a research project, OFH is likely to side-step any processes set up to assess or regulate PRSs, including their predictive value or cost-effectiveness (see Section 10). This could have major implications for NHS resources, and potentially shift control over treatment decisions away from doctors, to algorithms controlled by private companies.

In the USA, the Broad Institute (of MIT and Harvard) is one of the main research centres with a vested interest in the commercialisation of PRSs. An article describing the work of some of its researchers includes a footnote that they are "*co-inventors on a patent application for the use of genetic risk scores to determine risk and guide therapy*".[539] It is now common for academics working in this area to declare 'competing interests'. For example, one US study of how to report PRS results to patients in the US eMERGE network, lists interests of seven of the authors in 18 different companies, although these researchers are based mainly at the Broad Institute and other academic institutes as well as hospitals in Boston.[540] Whilst this paper cites a number of serious concerns (discussed in Section 5), its recommendations mainly focus on report design, without questioning whether PRSs should be fed back to individuals in the first place. A second paper on the proposed feedback of genomic risks by the eMERGE network bases its selection of ten PRSs to return to participants on the existence of odds ratios greater than 2 in the 'high risk' category (defined as 2 to 10% of the population, depending on the condition), despite such odds ratios being associated with very poor predictive value (see Section 5). The PRSs are developed through a partnership with the Broad Institute and multiple authors declare conflicts of interest which include links with commercial companies including 23andMe, Allelica and Illumina.

Big computing companies also have an interest in genomics. For example, Microsoft and Amazon are expected to provide the cloud computing services for the pilot of the UK's 'Our Future Health'.[541] Google has interests in artificial intelligence (AI) and the analysis of genomes.[542] In the UK, the proposed handover of NHS patient medical records to US spy-

tech company Palantir has already raised significant privacy concerns(see also Section 11).[543,544] The vested interests of computing companies in storing ever increasing amounts of health and genomic data also raises important questions about the environmental impacts of biobanks and data centres.[545,546]

In addition to the role of specific companies, it is important to be aware of the broader context of healthcare. In particular, commercial interests could use PRSs to introduce new forms of bias in healthcare. Overuse of healthcare increases costs and can result in harm to patients because of overtreatment. A recent study found that higher amounts of overuse among US health systems were associated with investor ownership and fewer primary care physicians.[547] This is relevant because PRS algorithms used in healthcare systems, such as the UK's NHS, would inevitably undermine the role of doctors acting as gatekeepers to decisions on healthcare and put recommendations into the hands of commercial companies. Because the PRS computer algorithms used to calculate people's genetic risks are a 'black box', it is easy for them to biased in ways that benefit commercial interests and lead to overtreatment. Further, the algorithms are so complex, doctors and their patients will be unable to make any meaningful check of the basis for the recommendations that they make. And since they are aimed at healthy people, decisions will not be made on the basis of the symptoms that a patient has. For example, the PRS algorithms might make recommendations for unnecessary tests or treatments, which could be extremely profitable. Treating rich, healthy people for diseases that they're never going to get is likely to be a much better market for healthcare companies than treating poorer people, who are more likely to be sick.

10. Lack of regulation

The benefits and risks of taking genetic tests are critically dependent on whether the risk information is reliable and has adequate predictive value (the 'clinical validity' of the test) and whether it is useful to decide who should take the proffered advice and hence improves health outcomes (the test's 'clinical utility'). There is widespread agreement on the standards that genetic and genomic tests should meet: however, there is currently limited monitoring or enforcement of such standards. This lack of regulation has been widely regarded as inadequate to protect consumers purchasing genetic tests sold direct-to-consumers (DTC) and users of genetic tests within health services.[548,549,550]

Recognition of this problem eventually led to the development of the In Vitro Diagnostics Regulation (IVDR) in the EU, and to action by the Food and Drug Administration (FDA) in the USA, which stopped some genetic tests from being marketed.[551,552] However, 23andMe's PRS for type 2 diabetes, which is sold directly to consumers (DTC), is not regulated by the FDA. This is because 23andMe chose to sell it as a 'wellness' product, which is supposedly not intended to make diagnoses and provide medical advice.[553,554] This loophole, which leads to some devices not being regulated, is problematic for both medical professionals and members of the public.[555,556] Another loophole exists for Laboratory Developed Tests (tests developed by a single laboratory) in the USA, which may also be exempt from FDA oversight.[557] The IVDR, which would require companies to provide evidence to support their claims, has not yet been implemented in the EU and future regulation in the UK is uncertain due to Brexit.

This means that there is currently no independent check of the claims companies are making about whether an individual is at high or low genetic risk of a particular disease. In the past (when fewer genes were included in the risk predictions), most commercial claims were demonstrably false.[558,559] More recently, the UK House of Commons Science and Technology Committee[560] and professional organisations such as the Royal College of Physicians and the British Society for Genetic Medicine have warned that the analytical

validity, sensitivity and clinical utility of direct to consumer (DTC) genomic or genetic testing may be much lower than is popularly perceived, and that for certain types of DTC results, there is a very high chance of false positive or false negative results.[561] This past experience, plus the lack of agreement between results from different algorithms (see Section 5), and poor reproducibility in different populations (see Section 7), should serve as red flags to warn that 'black box' algorithms used to calculate PRSs cannot simply be assumed to be correct, let alone to improve health outcomes. Although the developers of PRSs often claim they have solved earlier problems, there are still no safeguards to prevent false and misleading claims being made for PRSs. Because so many small effects on risk are combined into a single score, the algorithms are a 'black box' that is not straightforward to check. Unless these problems are addressed, members of the public will have no way of knowing whether results from PRSs are in any way reliable or useful for their health.

Some PRSs use machine learning approaches (sometimes referred to as Artificial Intelligence, or AI) in an attempt to improve predictions, but this also increases their complexity.[562] A recent review of medical applications of machine learning highlighted concerns that new machine learning models are being released after preliminary validation studies, without showing that they actually improve health outcomes in a 'gold standard' randomised clinical trial.[563] This adds to concerns that PRSs could be rolled out despite poor clinical performance.

Other than regulation, there are some other checks on what kind of information can be fed back to patients taking tests within health services. For example, in the USA, the American Medical Association makes recommendations on what tests can be used for screening, and insurers decide whether or not to pay for certain tests. The American College of Medical Genetics and Genomics (ACMG) has issued a statement warning that "*there is currently limited evidence to support the use of PRS to guide medical management*", but adherence to this statement is completely voluntary.[564] Companies such as Allelica and Genetic Technologies (based in Australia) are in the process of trying to convince US health insurers that they should pay for PRSs, in the context of assessing risk for cardiovascular disease.[565,566] In the UK, the National Institute for Health and Care Excellence (NICE) makes recommendations on new technologies introduced into the NHS, and the National Screening Committee (NSC) advises ministers and the NHS on population screening. However, plans to feedback PRSs from research projects such as the UK's planned 'Our Future Health' could effectively side-step these processes, allowing genetic risk predictions to be fed back to participants with no independent assessment of whether they are good for health, or cost-effective. In the USA, policies on the return of research results from genomic studies are still the subject of debate, and have tended to focus on rare genetic variants, rather than PRSs.[567] However, the eMERGE network (described above) also plans to return PRSs to participants. Internationally, a wide variety of policies apply to feedback of research results, and there is significant debate about how to handle the questionable validity of findings.[568]

Errors in much simpler algorithms (such as those used to recommend patients for liver transplants, or suggest calorie intakes for people who are overweight) have already been identified in the UK NHS.[569,570] However, to date, little attention has been paid to the likely consequences of errors and bias in PRS algorithms marketed by commercial companies. In particular, it remains unclear who might be liable for any harm to health.

11. Privacy, surveillance, commercial interests and the state

"*Someday we'll have a complete pedigree of the entire human population, and everybody will be connected to everybody on a huge family tree that looks like Google Maps*".
Professor George Church, co-founder of the Human Genome Project, 2009.[571]

There will be no secrets about paternity anymore". Professor Sir John Sulston, 2008.[572]

"*People have to recognise that this horse is out of the barn, and that your genome probably can't be protected, because everywhere you go you leave your genome behind*." Dr Jay Flatley, CEO, Illumina, 2009.[573]

"*In the wrong hands, US genomic data poses serious risks not only to the privacy of Americans, but also to US economic and national security*". Michael J. Orlando, Director, National Counterintelligence and Security Center, 2023.[574]

Rolling out Polygenic Risk Scores (PRSs) to whole populations requires the creation of vast DNA databases, linking individuals' biological samples (of their blood or saliva), to their genetic information (extracted from their DNA) and their medical records. Like fingerprints and iris scans, DNA is a 'biometric', i.e., it provides a biological measurement that can be used to identify individuals. In addition, it can also be used to find a person's biological relatives, since families share some of the same DNA.

A person's genome is their whole genetic make-up, but individuals can also be identified from smaller amounts of genetic information, including the information used to calculate their PRSs. If this genetic information is stored in a vast database, this can be used to track every individual and identify their relatives, including finding non-paternity.

A 2022 investigation of Direct to Consumer (DTC) genetic testing companies by Consumer Reports in the USA found that they employ policies and practices that their experts regarded as unnecessarily compromising privacy, with particular concern about the risks of opting in to data being shared for research.[575]

A 2022 study by the British Medical Journal (BMJ) found that hundreds of organisations (pharmaceutical companies, private healthcare providers and universities) had breached NHS patient data sharing agreements but not had their access to patient data withdrawn. "High risk" breaches involved handling information outside the remit agreed in data contracts which could lead to breaching confidentiality.[576] Currently, genetic data is not stored in electronic medical records in the UK NHS or other health services, but this is expected to change if PRSs are rolled out to the whole patient population. Because genetic information is a biometric, it can be used as an identifier, and unlike non-biometric information (such as an NHS number) it can't be changed if it is compromised. In addition, genetic information can identify a person's children and grandchildren, hence security is important over the very long term. This may be difficult to maintain in the context of new technologies (such as quantum computing, which some believe may compromise encryption). [577,578]

Even if such DNA databases can be kept secure (which is extremely doubtful in the longer term), the return of PRSs to individuals means that security is much more likely to be compromised. Once shared with individuals (for example, via apps on mobile phones), genomic data will be at risk of being shared more widely or of being hacked. This information will also be available for commercial exploitation by commercial companies who have access to the data (for example, by selling products to people supposedly at 'high genetic risk', or identifying and marketing products to the relatives of people who are sick).

A person's genome (or a panel of SNPs from a DNA chip) is sufficient to identify an individual (like a 'genetic fingerprint'), so this data cannot truly be anonymised. The disclosure of limited other information, such as health diagnosis codes, alongside a persons' genome, may be sufficient to identify them by comparing DNA sequences from a research project with electronic medical records.[579] Based on genetic information alone, in the

absence of any identifying information, an individual can be identified if their relative is in a genetic database, even if they themselves are not, because people share parts of their DNA with their families.[580] In the USA, there is already sufficient information in public genetic genealogy databases to deduce the identity of many individuals by triangulating other information such as surname, age and state.[581] Alternatively, an individual's surname can sometimes be deduced from information about DNA on the Y-chromosome that is passed down the male line (although such deductions will not always be correct).[582, 583]

Governments, security services and police will also be able to access genetic information, although in many countries they will need an order from a court.[584, 585] Laws that currently limit police access to such databases can easily be changed by future governments. Access to genetic information is unlikely to be restricted to a single country: for example, a recent example showed that using a genetic test provided by a Chinese company is likely to mean genetic information is sent to China.[586] In the USA, concerns have been raised about potential Chinese state access to the genomes of American citizens.[587] However, risks of 'genomic surveillance' are relevant not only under foreign or authoritarian regimes but also under democracies.[588] Since genomic data is expected to be shared internationally, individuals (including political dissidents, for example) could be tracked down wherever they are, and their relatives could also be identified and targeted. In many countries, women could be in danger if non-paternity is exposed, families could be broken up, vulnerable people (such as people on witness protection schemes or fleeing domestic violence) could have their identities exposed, or powerful people could be blackmailed if children born outside marriage can be identified.[589,590] In addition, categories derived from statistical analysis of genetic data (such as 'genetic ancestry', predicted health risks, or claimed genetic propensities to certain behaviours) can lead to stigma and discrimination (see Section 8).

The privacy risks associated with genetic studies increase as they grow in size and attempts to protect privacy are undermined by plans to give polygenic risk scores (PRSs) to individuals, perhaps linking them to their electronic medical records, or allowing them to be stored on people's mobile phones. For example, as discussed in Section 9, in the UK there are plans to provide PRSs to over 5 million people in the National Health Service (NHS), as part of a new partnership between the NHS and private companies, called "Our Future Health".[591] The project protocol states that data will be held securely in a Trusted Research Environment (TRE), based in the Cloud (likely using a Microsoft datacentre, with backups by Amazon, according to p.68 of the project's protocol), rather than on the project's own servers (as has been the case with the existing genetic research projects UK Biobank and the 100,000 Genomes Project). There are plans to provide copies of the TRE to (unspecified) commercial partners, who can then access the data directly and share it further with others (p. 64 of the protocol).[592] In effect, the project will use the NHS to recruit participants to provide genomic and health data to private companies. Although the project will resist access by the police, the protocol (p.61) accepts that this cannot be guaranteed.

As noted above, other studies are looking into the possibility of sequencing the genome of every baby at birth: these proposals are not discussed in detail in this report (because their main focus is on genetic disorders, not PRSs), but they would raise similar privacy concerns, exacerbated by the fact that babies cannot consent to the storage and use of their own DNA.[593,594] Many of these projects propose storing genomes for life, so the feedback of PRSs could happen in the future.

In the UK, the sharing of NHS medical records (without genetic information) is already controversial, with US spy-ware company Palantir believed likely to win a new contract to create a new database.[595,596] Intelligence agencies are increasingly buying private datasets and using software such as Palantir's to analyse the data.[597] The NHS is also working on a plan to outline how NHS genomic data can be made interoperable with other NHS systems

data.[598] Concerns raised in the UK about the potential handover of NHS patient medical records to Palantir would be exacerbated further in the future if these records included genomic data which could potentially identify every individual and their relatives.

Genetic information is generally not valuable unless it is linked in a database with people's names and addresses and other personal information. So, just leaving your DNA on a coffee cup, for example, is not sufficient to identify or track you and your relatives, if a database linking your DNA to your personal information and/or that of your family has not been set up. However, if your relatives are on a DNA database, you might still be identified even if you are not on the database yourself, because you share some of your DNA with them.

Currently, most people do not have genetic testing, unless it is directly useful to their health, and, even then, usually only small parts of a person's DNA are tested. Hence, calculating PRSs for everyone, or for a large part of a given population, would create a new system of surveillance on an unprecedented scale.

12. Conclusions

Using Polygenic Risk Scores (PRSs) in a population requires that everyone will have their genetic information and medical records stored in a vast database, potentially allowing every individual and their relatives to be identified and tracked. Advocates of this approach have sought to justify this level of surveillance by misleading claims about the future benefits to health.

However, Polygenic Risk Scores (PRSs) are highly controversial amongst scientists and the medical profession.

The idea that calculating every individual's genetic risk of developing common, complex diseases will be good for health is highly questionable because:

(i) Polygenic Risk Scores (PRSs) are poor predictors of common diseases and many people will be wrongly categorised;

(ii) Identifying large numbers of people as 'at high genetic risk' could lead to overtreatment and the marketing of medicines and other products to these people and their families and divert healthcare resources;

(iii) Computer algorithms calculating risk are extremely complicated and difficult to check. The companies which write the algorithms will have unprecedented power to decide who is at 'high genetic risk', and thus to decide the size of the market for medicines and other health-related products;

(iv) Major improvements in public health require social and environmental improvements for everyone, not just a minority with particular genes: for example, making sure that everyone can eat a healthy diet and breathe clean air. Targeting lifestyle advice at people identified as at 'high genetic risk' for particular diseases will not improve the health of the population as a whole, or tackle inequalities;

(v) Predictions of a person's risk of common diseases will always be limited by the complexity of these diseases, the limited importance of genetic differences, and the role of chance and other factors, including social and environmental ones;

(vi) Different PRSs give widely differing results, with very high uncertainties, raising questions about whether people can really trust the algorithms, and how they will be regulated;

(vii) Calculating PRSs is leading to racial categories being used in medicine in ways that could be dangerous and misleading, and that distract from the impacts of health inequalities and racism on health;

(viii) PRS risk predictions will be even poorer for people outside the 'European ancestry' populations that are the subject of most studies, but this does not mean

that more genetic studies to develop PRSs in different populations are a good priority for health;

(ix) A focus on genetic factors in late-onset common diseases undermines better public health priorities, such as tackling the socio-economic and environmental factors that underlie most cases of disease, and leads to the imposition of the wrong research priorities on poorer communities and in lower-income countries.

Computer algorithms based on adding many small effects can give widely different answers, depending on who is included in computer databases and what assumptions have been made. Most people who are told they are at high genetic risk will never develop the predicted disease, so PRSs could lead to unnecessary treatment of those identified as at high genetic risk. In addition, most people who develop one of these diseases will not be categorised as at high genetic risk for that particular disease, so the majority of cases of disease will not be prevented using this approach. Many diseases could be prevented or delayed by a focus on healthy lifestyles for all, and tackling inequalities and pollution, regardless of the genes that people have. There is a risk that creating costly genetic databases diverts resources, and acts as a major distraction from creating a healthy environment for all. In essence, more and more advanced technology is used to study more and more trivial issues, while the major population causes of disease are ignored.[599] This problem would likely be exacerbated in poorer countries, where PRSs are an even worse priority for health.

In addition, PRSs are largely unregulated, so individuals can be misled about their risk and make medical decisions based on erroneous results. PRSs are generally much worse predictors of disease than risk predictors based on other types of (non-genetic) information, and there are very large uncertainties in the predictions made for each individual. Different computer algorithms make wildly different predictions of risk for the same person. Further research is unlikely to improve the predictive value of such tests, which is limited by the low heritability of most of the relevant diseases and the complexity of the interactions between people's biology and their environment. In reality, increasing recognition of complexity is likely to reduce (not increase) the predictive value of future PRSs as more research is done.

Enthusiasm for PRSs is driven largely by commercial companies, who have vested interests in expanding the market for genetic testing, and gaining control of the genetic information of whole populations. There is potential for a massive expansion of exploitative marketing of drugs and other products to healthy people and their relatives, based on their claimed genetic risks. In addition, vast genetic databases could allow every individual and their relatives to be identified and tracked, and non-paternity to be identified, and will waste resources that could be better spent elsewhere. This contrasts with a more targeted approach in which genetic tests are used only when they are clinically relevant.

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