What if we had whole-genome sequence data for millions of individuals?

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The affordable whole-genome sequence is (nearly) here and already costs less than many commercial DNA tests for specific variants or genes. It seems very plausible to us that in the near future millions of people will have their genome sequenced, not just because the cost is coming down but also because individuals (in rich countries) are increasingly becoming ‘health consumers’. Here, we muse on what we could infer from having whole-genome sequence data for a million individuals.

In the absence of phenotypic data, there are six types of information that people can obtain from their own genomes. Firstly, their ancestry: how their chromosomes compare with those of typical members of diverse human populations. Secondly, things they can do something about (for example, enzyme deficiencies, BRCA1-like mutations, their pharmacogenetic responses). Thirdly, things they are unable to do anything about, most of which will be a source of anxiety [1]. Fourthly, things that explain interesting or medical phenotypes (for example, eye color or rare congenital traits). Fifthly, things they may worry about handing on to their children (and which they might want to check in their (prospective) spouse or prevent their children from being at high risk for). Finally, things they may like to pass on to their children.

**Actionable Mendelian variants now and in the future**

Although recessive Mendelian diseases are rare in the population, the number of carriers is always orders of magnitude larger than the number of homozygotes. For example, for a recessive Mendelian disease with a prevalence of one in a million, we would expect to find a single person who has the disease among our sample of 1 million people whose whole genomes were sequenced, but we would also expect to find about 2,000 people who are carriers. If we were to check their spouses, then on average 1 in 250,000 couples would discover that they are both carriers. These frequencies are just for one very rare disease; in fact, more than 1,000 genes have been identified that cause recessive Mendelian diseases and each person is a carrier for a number of these [2], so that about 1 in 25 couples can expect to discover that they share at least one mutation that has a non-trivial chance of resulting in their offspring having a severe congenital disorder. It seems likely that many individuals or couples will avail themselves of the opportunity to prepare for this possibility by having their genomes sequenced.

**Limits of disease susceptibility prediction from sequence data**

For common diseases, it will soon be possible to generate genomic risk profiles from the genome sequence, using existing knowledge from genome-wide association studies (GWAS) about multiple risk variants for a disease or complex trait. Prediction of individual risk of disease is not accurate at present because, for most diseases, only a small proportion of genetic variation in risk between people has been accounted for by known genetic variants. There is also a limit to how well a genetic predictor can ever work [3,4] because common disease is caused by the combination of genetic and environmental factors.

For complex traits, the upper limit of the correlation between an as-yet-unobserved phenotype and a genetic predictor for an individual is \( h^2 \), the square root of the proportion of phenotypic variation that is attributable to genetic variation (or the trait’s heritability \( h^2 \)). For most complex human traits, \( h^2 \) falls in the range of 40 to 80%, so the upper limit of the precision of prediction is about
likely that they will get these diseases. In this light, important than having the knowledge that they have someone ever gets diabetes or coronary disease is less personal fitness, it is more about skewing the odds than provided by software applications that aim to promote health action plans, and indulging in the self-knowledge For the millions of individuals who are assembling whether it is prediction or classification that matters. To some extent, this comes down to the question of from the study of millions of genomes? What might be the utility of risk scores derived from the study of millions of genomes? For quantitative traits and disease, we can expect major advances in our ability to explain the genetic component of disease risk and thus to predict disease. What we do with that information is a sociological concern with major public health implications, and now is the time to contemplate the implications. What if the millions of sequences came with detailed phenotype data? For example, this could comprise disease status for a range of common diseases and measures on quantitative traits that are risk factors for disease. This is not a far-fetched scenario. The Kaiser Permanente and University of California, San Francisco (UCSF) collaboration [8] has obtained detailed phenotyped and genotyped data for over 100,000 people, and earlier this year, it was announced that the UK Biobank sample of 500,000 people will be genotyped using a single-nucleotide polymorphism (SNP) array [9]. Phenotype and sequence data for a million people will allow the discovery of more risk and trait variants and the creation of multiple-variant profiles that can be used for prediction. But is a million sequences enough? For diseases with a prevalence of about 1%, there will be 10,000 cases among the million. Larger GWAS samples already exist for some diseases, such as Crohn’s disease and schizophrenia. Although these have identified tens to hundreds of risk variants, polygenic profiles explain only a modest proportion of risk in the population, although they can do better than self-reported ‘family history’ [10]. Sequence data (instead of solely relying on common variants from GWAS) will improve the prediction of disease by capturing variation resulting from lower-frequency risk variants. With millions of genomes sequenced, the limitation of disease prediction for many traits is likely to result from imperfect information on environmental effects. The question is therefore not ‘how well can we predict disease’ but ‘how can we incorporate probabilistic predictions of disease in personal or clinical decision making’. There are plenty of challenges on the way, including the generation of accurate sequence data, getting all these data together for analysis, and the statistical analysis of millions of genome sequences. Then, there will be the practical challenges of disseminating the results, not to mention encouraging people to act on them for the benefit of their health.

For quantitative traits and disease, we can expect major advances in our ability to explain the genetic component of disease risk and thus to predict disease. What we do with that information is a sociological concern with major public health implications, and now is the time to contemplate the implications.

**Abbreviation**
GWAS: Genome-wide association study.

**Competing interests**
The authors declare that they have no competing interests.
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