Bioethics: a look into the future

GENOMICS AND ETHICS

Chris Willmott

I am delighted and honoured to join in the celebration of this landmark anniversary in the story of the Víctor Grífols i Lucas Foundation. Some of the most exciting developments in biomedicine during the past 25 years concern our ability to sequence the complete genome of humans (as well as other species) and the applications that stem from that capacity. In this chapter, I am going to review some of those uses and draw attention to potential ethical issues associated with the exploitation of this data.

Back in 1998, when the Grifols Foundation was established, the official human genome project (HGP) to capture the full genetic sequence of humans was already well under way. Interest in this ambitious and expensive project to lay out in order all three billion letters in the *handbook of mankind* had gained traction from the mid-1980s, and the co-ordinated work of the International Human Genome Sequencing Consortium had begun in earnest in 1990. The year 1998, however, has significance in the rise of genomics for two important reasons. Firstly, it was the year that those official partners implemented the so-called Bermuda Principles in which they pledged to make as much of the sequenced DNA data freely available as quickly as possible after it had been determined. This openness represented a paradigm shift, in stark contrast to some of the original pitches for the work, where profits from biotechnological spin-offs were dangled in front of potential investors. Secondly, 1998 was the year that Celera Genomics, a rival to the official HGP, was established. Under the leadership of Craig Venter, Celera initially proposed a profit-driven approach, with access to their data offered on a pay-per-view model (although this too was subsequently liberalized).

Celera promised, and delivered, DNA sequencing faster and more cheaply than had been the case up to that point. This was, in part, derived from the fact that they could exploit the existing mapping carried out by the main HGP as a scaffold in which to fit their data (a bit like having their rivals prepare the picture on the lid of the box allowing them to solve the jigsaw puzzle more quickly). More significantly, however, they offered a radically streamlined method for the sequencing itself. They dispensed with the costly and time-consuming steps of archiving human DNA in bite-size genetic cassettes, stored within bacteria. Instead, they employed a "whole-genome shotgun sequencing" in which they essentially smashed all of the chromosomes into bits around 500 bp (ie 500 letters) in length, which they sequenced directly.

Initially there were significant tensions between the two factions. However, an uneasy truce was called and a deal was brokered in which they both published their draft results on the same day (in 2001). The corrected versions were published in 2003 (though for technical reasons this was still only 92% of the whole. The full sequence, including the tricky bits, not completed until April 2022).

The new Celera approach had transformed sequencing. However, even this cheaper and quicker methodology would still have struggled to deliver some of the health benefits that had been promised as justification for the vast expenditure poured into this big science project. This work, taking many years, at the cost of hundreds of millions (for the Celera approach) even billions of dollars (for the official HGP) had succeeded in producing a reference copy of the full

human genome, but it was derived from only a handful of individuals (only around a dozen, across both projects). Of course, the interesting aspects of genomics for us as individuals, the factors that inform both our health risks and our family relatedness, are our distinctives. It has been estimated that for each of us, our DNA deviates from the reference genome by about four million letters. The key benefits of genomic medicine are the capacity to offer personalized medicine, diagnosis and treatments tailored to the specific needs of a patient. These need to be made available in a matter of hours or at most days, at a fraction of the previous costs. For the full potential of this work to be unleashed there would need to be a fundamental change in the way that genomics was done.

Those essential technological advances have now been delivered. Today, DNA can be sequenced using a variety of methods, sometimes grouped under the umbrella term Next-Generation Sequencing, which are fundamentally different to the techniques used for completion of the HGP. Here is not the place to go into the exact details, but the key is that thousands, often millions, of tiny sequencing reactions are set off in parallel. By 2010, it was already estimated that sequencing was 50,000 times faster than it had been in 2000, and in 2022 a human genome was completely sequenced in five hours.

Similarly, the costs have also plummeted. From hundreds of millions or even billions of dollars per human genome, it is now feasible to get a read-out of someone's whole DNA sequence for a few hundred dollars. These advances combined have opened the door to the post-genomic era – a world of radical opportunities that match and then far exceed the original promise of the HGP. In this next section, I intend to give a swift overview of some of those diverse applications, before drilling down more closely into three of them.

APPLICATIONS OF GENOMICS

Beginning away from specifically human or medical applications, it is now feasible to revisit ideas of the relatedness of species by examining their DNA rather than their physical features. This phylogenetic approach has led to radical rethinking about taxonomy.

By looking at the genetic differences between species, we can also gather very useful clues about the potential function of particular genes. For example, in one study, researchers took the apparently unlikely step of comparing the human genome (which includes code for hair-like structures called cilia), with the genome of a single cell organism called *Chlamydomonas* (which has similar hair-like flagella) and the plant *Arabidopsis* (which has neither). By looking for genes that were present in both humans and *Chlamydomonas*, but not in *Arabidopsis*, they were able to radically shorten the list of potential genes responsible for a cilia-related disease.

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Other comparisons might look at the genomes of a bacterial species which remains susceptible to a given antibiotic and another from the same species which has developed resistance to that drug. By doing so, they can gain insights into the molecular basis of the medicine's loss of efficacy against that organism (and potentially identify ways to overcome the problem). Similarly, we have all seen the ways in real-time sequencing of their genome gave valuable insight into the evolution and spread of the Sars-CoV-2 virus variants in the COVID-19 pandemic (albeit by slightly different methods, since the virus has an RNA genome).

METAGENOMICS

Elsewhere, by trawling an environment for traces of DNA, it can be possible to identify the species living in that habitat, even if you have not seen them. Craig Venter, who we encountered previously in the context of Celera's rival approach to the HGP, famously set sail around the world in his yacht *Sorcerer II* capturing onto filters the DNA from microbes in the oceans he passed through, in order to map the occurrence of known species and give hints of previously unknown organisms. Aside from the inherent curiosity about our world, some of these species might ultimately prove to be useful sources of new medicinal drugs.

Transfer this kind of genomic approach to the human gut, and we are back onto applications of direct medical benefit. There is growing recognition of the impact of the microbiome, species of bacterial and viruses living in our intestines, on our general health. Previous attempts to identify these organisms often floundered because scientists could not work out conditions to grow them in their laboratories. Now a *metagenomic* approach can be used, in which all of the DNA in the gut is sampled simultaneously. This complicated mixture won't easily yield detailed analysis of the genome of any one organism, but by looking at a particular gene that is known to be constant within any given species, but different between species, you can at least identify which bacteria are present.

Finally, let us look in details at three applications of genomics – personalized medicine, whole genome sequencing of newborns, and the rise in user-initiated or direct-to-consumer (DTC) genetic testing. As well as surveying the potential of these approaches, we will also consider the ethical issues that they raise.

DIPPING INTO YOUR DNA RECORDS FROM YOUR OWN HOME

For most people, the first place they are likely to encounter the power of contemporary genomics is in the form of a genetic test they can conduct at home. By 2020, it was estimated that over 30 million people had already taken a test of this kind. Some will have bought them for themselves, most likely out of curiosity about their heritage (the company Ancestry had delivered about half of the tests done

at that point), although some may have had medical motives. Others will have had a test bought for them, maybe on the promise of knowing what percentage Viking they would turn out to be.

The ease of access to such tests belies the significance that the results might hold. Whilst knowledge of our genes is potentially empowering, for example if it was to reveal a previously undiagnosed medical condition where treatment was possible, there are a number of significant issues that might arise. The most well-known hazard comes when there is a revelation that someone is not, in fact, biologically related to one or both of the people they have considered to be their natural parents.

On the flipside, the ability to connect with genetic relatives is one of the attractions of home genetic tests – for example, adoptees and those who know that their biological father was a sperm donor are able to forge networks of half-siblings. Others too are looking to make identification via these databases. The arrest and unmasking of Joseph DeAngelo as the *Golden State Killer*, responsible for a series of rapes and murders in the 1970s, is the best known example of police screening genomic archives to assist in solving crimes, but this is becoming a routine aspect of inquiries.

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WHO'S RIFLING THROUGH YOUR GENES?

This raises further concerns about who has access to the genetic information users of DTC sites are handing over to the companies. As we have discussed, the expense of testing has plummeted. However, the fact that some services are offering tests for lower prices that it costs to conduct and process the results ought to be a warning that they are recouping their expenses via other means, for example selling your data to third parties. Add to this the possibility of company buy-outs or of data breaches and you reach a situation where it would be best for users of any DTC service to assume that their genetic information is now openly available to other interested party. Are clients sufficiently aware of this when they sign over their consent?

Additionally, there can be questions about the accuracy of results. Mistakes in sequencing reactions are inevitable. For this reason, industry standards see regions re-sequenced at least 30 times to guard against such errors, and frequently there are 100 re-readings of the DNA to make sure the report is correct. Companies

offering sequencing at the lower end of budgets are likely saving costs by only doing a minimal number or re-screenings. This heightens the possibility of results being wrong, either false positive or false negative.

This risk is compounded by the fact that many DTC services still rely on older microarray technologies, where a series of DNA sequences are placed on a *gene chip*. Importantly, this approach involves pre-selection of the mutations being investigated (rather than WGS, where you see what emerges organically from the data). There is growing awareness that uneven distribution of ancestral backgrounds (genomes of Hispanic and African origin are notably under-represented) causes bias in the databases, and may mean important mutations relevant to particular populations are missed simply because the microarray is not set up to look for them.

All of which raises a final concern about DTC services, the lack of genetic counselling available to those who receive genetic information from these companies. What is the mutation is real, but the consequence of that change are not actionable, i.e. there is nothing we can do about this revelation, or will be late onset and irrelevant for many years? Talking people through the interpretation of their results carries an inevitable financial cost, and so counselling is not routinely offered to customers. This can cause them to be anxious and confused. It may leave them turning to more formal health providers (such as the NHS in the UK), passing the burden to the latter.

STARTING THEM EARLY

This leads us into more overtly medical territory, where the roll out of WGS for all newborn babies is actively being considered. Testing in the form of a small blood test, around five days after birth, is already routine in the USA and Europe. However, these only report on fewer than a dozen conditions, all of which are both significantly detrimental if untreated and where knowledge that the child has the fault can facilitate appropriate intervention. Collecting the full genomic information from a baby would be a very different prospect.

Expansion of screening in this way would shine an early spotlight on a far broader range of conditions including rare diseases which might not otherwise be identified for many years. In theory it creates the possibility to produce a genetic passport which the individual could make available to their doctors throughout their lifetime. Proponents are also overt about the research benefits for wider society that would be facilitated by such a systematic collection of data.

Many of the potential risks are the same as we have already seen for DTC testing. These include paternity issues, and concerns about who will have access to the information, both now and in the future. As a state-run scheme there is the added worry that

a future dictatorship might abuse the data to victimize a subsection of the population.

There are additional issues in regard to consent. Clearly the infant cannot be asked to give permission for their own checks, and the parents are the obvious proxy. Questions have already been raised about how much parents understand the existing heel-prick tests, since consent is often taken by a midwife as part of barrage of questions at the point where they are somewhat distracted by the exertions of the birth and excitement about their new arrival. And what happens if the parents disagree? What is the default position? Who has the casting vote? What if the child, when they become old enough to offer their own views, wishes to remove their genetic records from the database —will this be feasible?

Some results emerging from newborn screening might be of instant importance, others might only have relevance later in life. Do the parents get informed about these, when it might negatively influence their bonding with the child throughout the latter's whole life? What if that information only had significance so far into the future that the parents might already be dead? And what about the fruits of future research? If gleaning more information about the genetic basis of disease is one of the stated benefits of neonatal screening, then it is probable that some results will gain greater relevance than is initially understood.

Would there be a commitment to update everyone as soon as relevant findings are discovered? It is highly likely that emerging significance will relate to so-called polygenic risks where the interaction of multiple genes, combined with environmental influences, rather than to Monogenic disorders where mutation in only one gene is the determining factor. Since lifestyle choices might well be part of the mix, surely an individual needs to know their status as soon as possible so they can make any necessary changes, e.g. to their diet. However, this would be an enormous logistical and financial undertaking, so perhaps a scheduled update every few years is more realistic.

MAKING PERSONALIZED MEDICINE

If discussion about the pros and cons of newborn screening remains slightly future-focused, let us conclude with one application of genomics that has definitely arrived. In various specialisms, the promise of targeted treatment, tailored to the underlying genetic cause with the specific patient has become feasible. The potential for this approach is most evident in tackling cancer.

If statistics are to be believed, most readers will have had an encounter with cancer, either personally or affecting a close family member or friend. You will know that treatments up until now have tended to be aggressive and non-personalized —a sledge-hammer to crack a nut. Radiotherapy and chemotherapy exact a

huge toll on the patient. Whilst such approaches have certainly not been consigned to history, they are starting to be replaced by more specific treatments.

Cancers are fundamentally genetic illnesses, caused by an accumulation of errors over time. Whereas description of a cancer was previously restricted to identifying the tissue in which it was found, for example in the liver or on the skin, and possibly the sort of cells in which it originated, it is now feasible to detect the exact genetic changes that have led to the condition. This opens up the possibility of giving one or more drug that will only kill the mutant cells, not the healthy ones. For example there are now known to be at least ten different subtypes of breast cancer. Some medicines would be ideal to tackle some of these, but useless or even harmful to patients with different forms.

This molecular understanding is also revealing that the underlying cause of cancer in one patient might be the same as the disease found in a different organ for another. When this is the case, it has been demonstrated that a medicine to treat one form of cancer might be applicable to the second. In one example, the drug Vemurafenib, developed to fight skin melanoma, also proved effective against certain types of blood cancer, once it was shown that a crucial genetic change was the same in both cases. This ability to repurpose existing drugs can bring about effective treatment far more quickly than having to start from scratch for the identification and licensing of a new compound.

Ethically, treating someone with a more effective medicine seems like an easy win. Of course, life is not that straightforward. Many of the targeted treatments are spectacularly expensive, and so may be beyond the reach of some patients or health care providers. This brings us back to one of the crucial dilemmas in all of these genomic approaches, disparity of access. Whilst this cannot be grounds for holding everyone back to the lowest common denominator, it is nonetheless a reminder of the need to ensure that the benefits of these technologies are shared as widely as possible, and as quickly as possible.

SUMMARY

The next few years are going to see further growth in the realization of genomic approaches in medicine, and further afield. The potential is revolutionary and exciting, but there are ethical questions that will need to be constantly monitored. These include: the accuracy of results; dealing with unexpected findings; whether anything can be done in the light of any genomic revelation and the cost of doing so; equality of access; and the provision of necessary counselling. There therefore remains plenty for the Grífols Foundation and others to consider during the coming 25 years. ///