Genomics in our own hands

After the announcement of the first draft of the human genome sequence, personalised medicine became a major aspiration for the future. Armed with our own genomic information, we supposed, we could predict our disease risks and customise drugs and care to suit. So, how far has personal genomics come in the past 10 years? Ruth Williams investigates.

On June 26, 2000, in the East Room of the Whitehouse, Washington DC, USA, Bill Clinton, together with Francis Collins, then leader of the publicly funded human genome project, and Craig Venter, then head of Celera Genomics, announced to the world the completion of the rough draft of the entire human genome. It had taken more than a decade of globally concerted efforts and several billion dollars to reach this pivotal moment in scientific history.

The exact cost of producing that first draft is almost immeasurable, but the material costs of sequencing at the time were "getting down to around about 10 cents a base", says Michael Morgan, special consultant to Cold Spring Harbor Laboratory, NY, USA, and ex-chief executive of the Wellcome Trust Genome Campus, Hinxton, UK. "People don't talk in those terms any more", he says, "they talk about the cost per genome." At 10 cents per base, 3 billion base pairs of DNA—the size of the haploid human genome—would have cost US$300 million. "These days we're talking about $100 000", says Morgan.

The cost is even lower than that according to George Church, professor of genetics at Harvard University, Cambridge, MA, USA. Church is co-founder and chief scientific officer of the genomics company Knome, which, he says, will sequence and interpret an individual's whole genome for about $60 000. Alternatively, they will sequence just the coding portion of the genome (the exome) for $20 000.

The cost of sequencing, although clearly plummeting, is still prohibitively expensive for most people. So what can members of the general public do if they want to take charge of their genetic information now and find out what lies in store disease-wise in their future? And, what, if anything, can they learn?

Instead of sequencing a person's whole genome, for a price of between $400 and $2000, companies such as 23andMe, deCODEme, Navigenics, and Pathway Genomics will pick hundreds of thousands of tiny points in the genome and look only at those. The chosen points are a combination of known disease mutations and single nucleotide polymorphisms (SNPs)—common variation points at which either one of (normally) two nucleotides can be found. Scientists have discovered that, depending on which nucleotide an individual has at a given SNP, their risks for a particular disease or for an adverse drug reaction can vary.

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A $400 kit that can be used to assess an individual's risks for many different complex diseases and adverse drug reactions, as well as their carrier status for certain known disease mutations, is arguably a bargain. Faced with the test results, however, the individual might question whether the money was so well spent. "At the moment this is not much better than snake oil medicine", says Morgan, "in the sense that one is dealing with probabilities, which, for the average person, are almost completely meaningless."

The results are indeed mind-boggling, even for those familiar with genetics. The most straightforward of the results are those for carrier status. For example, if you have one of the mutations in the *ASPA* gene, for which 23andMe check, and if your partner carries one too, according to basic mendelian genetics, your offspring have a 25% chance of developing brain-degenerating Canavan disease. However, "You may still have a mutation that reduces ASPA activity or be affected by Canavan disease even if your data indicate that you are a non-carrier", reads the 23andMe website, no doubt for legal reasons, but somewhat worrying nonetheless.

More confusing are the results for risk of complex diseases such as cancer, multiple sclerosis, Parkinson's disease, and Alzheimer's disease, for which a mix of many possible genes and environmental factors are thought to be involved. For example, on the basis of whether or not you possess a very rare SNP variant, your risk of Parkinson's disease might be increased by 2·9 times. Most people who develop Parkinson's disease, however, will not have this variant and many who do have it won't develop the disease. Furthermore, even if you discover that you have this variant, there is nothing that can be done to avoid the disease. A similar situation is true for multiple sclerosis. If you find you have one or multiple SNPs that confer additional risk, first you must unravel what that risk really means, and then there would be little point worrying because, should you develop the disease, your treatment options would be the same as usual. One particular test that 23andMe offers can reveal whether an individual faces an extremely high risk of Parkinson's disease (74% by age 79 years)—no doubt included in this company's kit because the husband of one of the

founders, Google developer Sergey Brin, has the variant. Again, however, neither Brin nor anyone else with the variant can currently change the possibility of a parkinsonian fate.

Although there are many tests for which the results are actionable—if a test reveals you metabolise caffeine slowly and thus are at an increased risk of a heart attack, for example, you can cut out the coffee—there are many tests, including almost all those for neurological diseases, for which no preventive action can be taken.

Even if nothing can be done clinically, says Joanna Mountain, senior director of research at 23andMe, "People who find out such information tend to discover ways to take action." For example, they might offer to participate in research, exercise more, or maybe educate themselves about the disease, she says.

A major concern is that, because doctors are not trained to interpret or advise about the results of these kits, the potentially confusing results might cause unnecessary concern or, perhaps worse, false reassurance—for example, a woman with no SNP variants associated with risk of breast cancer might become complacent about the need for regular self-checks.

Such concerns have led some European countries to ban sales of these types of kits, while in the UK, the Human Genetics Commission has published a set of principles to address the need for general international guidelines for their sale and use. In the USA, the Food and Drug Administration is investigating Pathway Genomics because of the company's plan to sell its kits in Walgreens pharmacies.

Kari Stefansson, president of deCODE Genetics, Reykjavik, Iceland, is tired of the criticisms and scepticism: "I don't understand the attitude! Personal genomics is nothing but a mechanism for people to learn about their own genetic background. How can it be bad for people to learn something about themselves? How can that not be of value for people?" With barely a break, he continues: "Why should people not have access to it? It's not just about getting information you can act on, it's about wanting to know about yourself." Neurologist Eric Ahlskog (Mayo Clinic, Rochester, MN, USA) agrees that it comes down to personal choice: "In an open society like ours, consumer options such as these are inevitable", he says.

Debates over the current kits are likely to continue for a few more years, until whole-genome sequencing is cheap enough to replace them, which won't be long. Sequencing company Complete Genomics says it is on target to achieve a price of $1000 (including profit) by 2014. This is mostly thanks to the economies of scale: "We are building capacity to sequence 500 genomes a month towards the end of this year", says Radoje Drmanac, chief scientific officer. The company does not currently sell directly to individuals but it is in talks with Knome. Both 23andMe and DeCODEme say they also plan to offer full genome sequencing in the future.

For people who can't wait, individual genomes can be sequenced for free by taking part in the Personal Genome Project organised by Church. However, individuals must be willing to share their medical history and photos of themselves with the rest of the world. The project aims to raise awareness of genome sequencing and is leading a trend. "There will come a day in the not too distant future when every person will have his or her genome sequenced as a routine part of medical care", predicts Francis Collins, now director of the US National Institutes of Health. Perhaps then, the present controversial kits are just a rather wobbly stepping-stone to that end goal. "We're in a period of change and people who are signing up for our service are basically a bit ahead of the curve", says Mountain.

By implication, Joseph Jankovic, professor of neurology at Baylor College of Medicine, Houston, TX, USA, and scientific adviser for the Parkinson's disease genetics initiative run by 23andMe, is a bit behind the curve: "I have a kit that was sent to me by 23andMe to have my genomic testing done free of charge", he says. "It has been sitting on my desk for about a year." He goes on: "First of all, I don't want to know, and if I did know what would I do about it?"

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Perhaps this is behind-the-curve thinking, but it is also a common reaction. Many people, arguably most, are at least a little uncomfortable with the idea of knowing they are at risk of a disease they can do nothing about. Even Kari Stefansson had some reservations: "When I did the test, the only one that made me really anxious was the one for Alzheimer's disease. I wasn't comfortable with it."

This anxiety and discomfort cannot be taken lightly when we reach the point of genome sequencing for everyone. "An argument could be made that the best time for most people [to be sequenced] would be shortly after birth", says Collins. "Such information could enable parents to take steps to reduce their children's risks of developing diseases and to improve their odds of living long and healthy lives." Although that is true, one question is, would everyone see this as a benefit that outweighs an individual's right not to know their future?

Ruth Williams
ruth.williams@absw.org.uk