The 100,000 Genome Project will put England in the vanguard of one of the most significant revolutions in medical history. But will the NHS be ready? **Craig Ryan** investigates.

Whole system change

What strikes you immediately about the 100,000 Human Genome Project is its scale. The numbers are big; like banking and astrophysics, the figures involved in genomics are mind-boggling to outsiders. The science is big; whether it's the biggest breakthrough since Lister's antiseptics, Jenner's vaccinations or Fleming's penicillin, everyone agrees it's a biggie. And the consequences for the NHS, for both clinicians and managers, are big too: so big, in fact, we can't get them into focus yet.

"The Ancient Greeks diagnosed disease by looking at the stars and the movements of planets," says Alastair Kent, director of Genetics Alliance UK and a member of the project's ethics advisory board. "In medieval times they talked about the four humours, then we got onto germs and viruses, and now we're looking at the molecular level. This gives us the opportunity to eliminate some of these really nasty conditions about which we've been able to do nothing since homo sapiens first appeared as a species."

The project itself – "100KGP" seems to be the accepted acronym – aims to sequence 100,000 whole genomes by the end of 2017. This means capturing the complete set of genetic information that makes up a human being — 3.2 billion "base pairs" of DNA. You don't need to know what a base pair is to see that's a lot of data.

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Sequencing the first whole human genome took 13 years and cost £2bn. Genomics England (GeL), the state-owned company formed to deliver the sequencing project, has three years and a budget of just £100m — although its partners, US genetics company Illumina and the Wellcome Trust, are investing another £190m in related infrastructure, technology and support services.

By any measure it's a tall order. "Don't tell the politicians too much about it, but it's a very challenging programme," said chief executive Sir John Chisholm at GeL's first public meeting at Barts Hospital in October. Yes, costs have fallen dramatically, but it still costs at least $5,000 to sequence a whole genome and analyse all the information. GeL is relying on a combination of technological progress and competition between sequencing companies to get costs down and the project over the line.

But the 100KGP is only part of a live process of experiment and transformation which will see research go hand in hand with implementing genomic

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medicine within the NHS. At least, that's the plan.

"I see it as very much a hybrid model that is both research and NHS transformation," says Tom Fowler, Genomics England's director of public health. "Making use of the clinical information in our systems to make us a world leader in research, while also feeding directly back to patients who will feel the benefits."

Ian Cumming, chief executive of Health Education England, which is leading on the huge workforce implications, says the sequencing project is just the tip of the iceberg. "I don't think it's over-hyped to say this is one of the biggest revolutions in the practice of medicine and healthcare that we've seen for many, many years. We're going to see an ever increasing shift towards the personalisation of healthcare… My personal view is that within seven to ten years, the NHS will be sequencing the genome of everyone who wants it."

Pharmacogeneticist Mark Bartlett, managing director of Geneix, which works with NHS hospitals on using genomic data, agrees. "That's the way it's going. It will be a resource to be mined at the point of care. So if a patient comes in with a difficult diagnosis, that whole genome can be looked at… The doctor will be able to prescribe medication that is right for the patient, not just for the disease."

An illustration of how genomics is moving, as Cumming puts it, "from bench to bedside", is a prototype device, about the size of a shoebox, which can sequence a small part of the genome and deliver results in just 15 minutes. This allows doctors to identify, for example, familial hypercholesterolaemia, different types of diabetes or whether an infection is bacterial or viral — and, if bacterial, which antibiotic will work best.

"That's where we'll be, certainly in five years," says Cumming. "And that's why we're trying to get ahead of the curve, and not do what we've perhaps done in the past, which is to have all sorts of new technology and new ways of working, and not have the workforce ready to use it."

The NHS will certainly need more clinical geneticists and bioinformaticians but HEE's education programme goes way beyond the specialist workforce. "If we think this is just about clinical genetics, we've got it wrong," warns Cumming. "This is about every clinician in the NHS.

"GPs are already telling me that they're being asked for advice from patients who have had part of their genome sequenced and are going back to their GPs and saying, 'what does this mean, doctor? Can you help me and talk me through it?'"

With its £20m slice of the budget, HEE is tendering a new MSc programme in Genomic Medicine, which Cumming expects to train about 500 people, and will fund some PhD and post-doctoral research. It will also offer more accessible training programmes, beginning with a two-hour online "Introduction to Genomics" course, open to all NHS staff.

The sheer volume of data is one of the biggest challenges. A single human genome will just about fit onto a standard hard disk, but is equivalent to millions of pages of text. All this has to be analysed, the interesting bits pulled out and put into a format that working doctors can use – 100,000 times over.

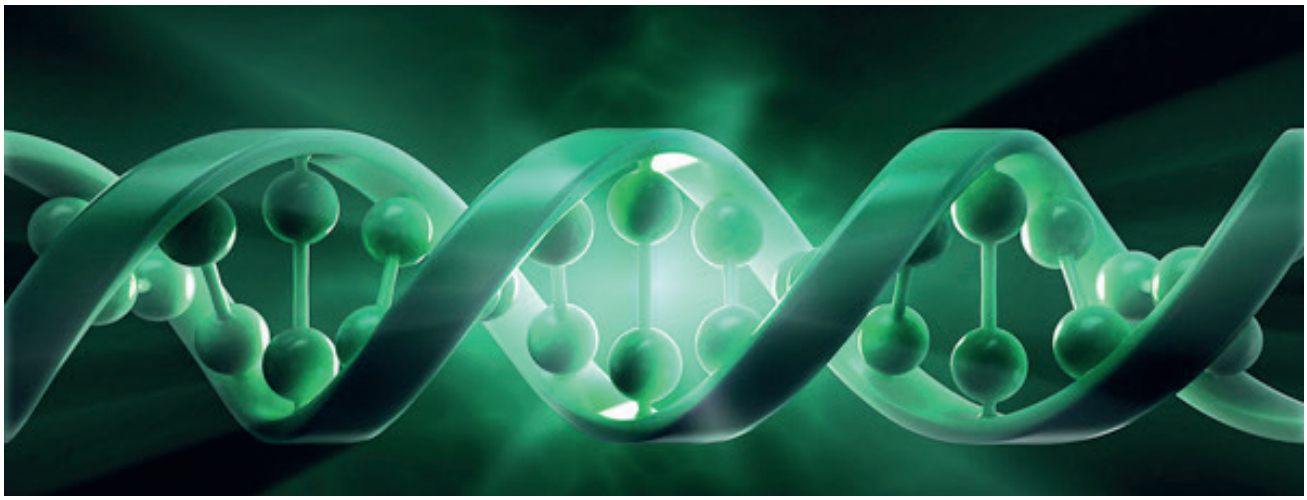
And it's not as if researchers are 100% sure what they're looking for. "It's a kind of Rumsfeld scenario," says Alastair Kent. "There are some things we know — that these mutations result in these outcomes. Then there are things where we're reasonably confident that there's a causal association between the genome and a particular event. And then there's an awful lot of stuff we just don't know — changes of unknown significance."

One of Kent's concerns is that patients who volunteer early for genome sequencing don't get left behind as the knowledge moves on. "We don't want them to get a 1.0 version of the interpretation when a 2.0 version comes along in 12 months' time," he says.

Kent also questions whether NHS structures will be able to keep pace with the political momentum behind the research project. "You have the prime minister breathing down your neck if you're on the board of Genomics England," he says. "So they're under huge pressure to deliver significant results very quickly. Our concern is that the short-term mechanisms will not be sufficiently robust to secure the sustainability of the project and transfer the knowledge into the NHS."

Trying to make sense of all the institutional architecture thrown up very quickly around the project is like trying

The prototype "genetics lab in a box" which can sequence part of the genome and deliver results in just 15 minutes.



to nail jelly to the wall. In particular, many insiders question whether NHS England is nimble enough to drive through the implementation of genomic medicine within such a fragmented system.

"To be honest, it's very difficult to get a sense of what's happening on the ground with NHS England, beyond the fine words of the chief executive," says a source very close to the project. "One hopes things are happening, but at the moment NHS England is so focused on achieving financial balance that other things have gone by the board."

It may or may not be significant that no one from NHS England was able to comment for this article.

A common misconception is that genomic medicine is all about genetic diseases. But our DNA also determines how all types of disease affect us and how we respond to treatment. Rare genetic diseases are an important part of the 100KGP – ironically, with 5,000 different types identified, "rare" diseases are actually quite common – but the research will also include patients suffering from cancer and infectious diseases.

Sequencing the whole genome is very different to the limited form of sequencing which goes on at the moment, where scientists concentrate on a few genes known to be connected with particular conditions or diseases. At GeL's public meeting, Peter Johnson, chief clinician at Cancer Research UK likened it to going from the Mappa Mundi to Google Earth in terms of understanding the genetic make-up of people and organisms like cancer.

"This is not about… genetic inheritance, it's about the changes that take place after birth and during life," he said. Sequencing has already revealed many more genetic variations of cancer than expected. "There's one particular type of lung cancer for which we have a blocking drug, which probably only affects 1% of people with lung cancer," added Johnson. "So, in some senses everything's becoming a rare disease."

Concentrating initially on the "difficult" cancers with very low survival rates – lung, oesophagus, pancreas and brain — researchers will compare the DNA of the tumour to the patient's normal cells, enabling the precise changes that cause the cancer to be detected.

But the most immediate impact is expected with the diagnosis and treatment of infectious diseases, says Fowler. "With TB outbreaks, for example, we can use this technology to understand the spread, the epidemiology behind it, and where it's come from. And that leads to a lot more you can do."

Back in 2012, genome sequencing was used to stamp out an outbreak of MRSA at the special care baby unit at Cambridge University Hospital, as well as to identify and treat the individual carrier. It's believed to be the first use of the technology to identify and eradicate an outbreak of an infectious disease.

Faster and more effective diagnosis will help to beef up the "value proposition" for genomic technology, particularly with often-sceptical commissioners, who will, ultimately, have to fund it. "It may well be already cost-effective to use this technology as opposed to the sort of diagnostic odyssey that patients often have to go through at the moment," says Fowler.

Mark Bartlett admits the "genomics industry" may have been guilty of "over-promising" in the past, but insists there is a genuine sense of optimism about the 100KGP, despite the daunting challenges. "I'm actually very supportive of what Genomics England are trying to do. I think they're taking a very realistic approach."

But moving technology "from bench to bedside" has often been a weak spot for the NHS, as it has for Britain generally. The NHS will need strong leadership, more funding and a better sense of vision if the blaze of promise represented by the 100KGP isn't to fizzle out in the day-to-day business of implementation. ■

HEE's two-hour online "Introduction to Genomics" course is open to anyone who works in the NHS. To sign up, visit: www.genomicseducation.org.uk/courses/introduction-to-genomics