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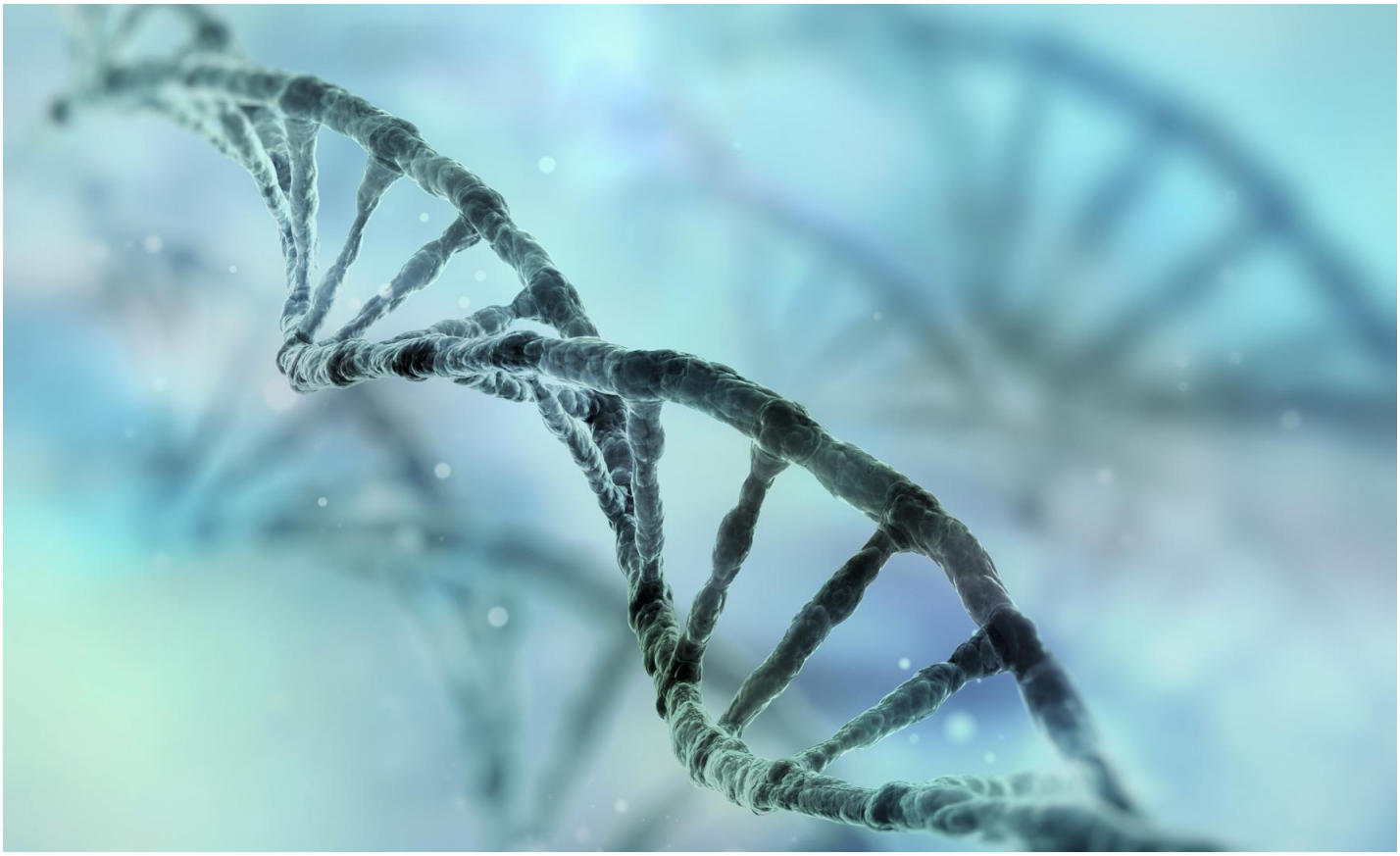

Getting personal with DNA

Part of our 30th anniversary series, Sagentia takes a look at some of the key trends in the last three decades and how these breakthroughs in science and technology have impacted the way we live and work today.

A Sagentia
white paper

Getting personal with DNA

This article takes a look at the way our understanding of DNA, genes and the human genome has improved over the last thirty years and has paved the way to the personalisation of forensics, medical diagnostics and medicine. It tracks the emergence of PCR for amplifying small amounts of DNA and the birth of the human genome project. It then goes on to look at how next generation sequencing has given rise to targeted treatments for specific patient sub-categories and explores what this might mean for drug innovation and precision medicine.

Early precision methods

Unbelievably it was only as far back as 1985, (the year before Sagentia's inauguration as Scientific Generics) that Professor Sir Alec John Jeffreys had what he calls his 'eureka' moment and developed a method for DNA profiling. By being able to decide whether genetic material comes from a particular individual, its subsequent impact has been huge - not only in identifying and prosecuting criminals for some of the nastiest crimes but also in helping to resolve paternity and immigration disputes. Jeffreys effectively developed a method to identify people from repeated DNA motifs that occur (almost uniquely) in different individuals.

This breakthrough moment occurred at about the same time as another key historical moment in this area – the arrival of polymerase chain reaction diagnostic (PCR) tests. In the early to mid-eighties, a team of Cetus scientists had conceived a method to create unlimited copies of DNA from just one original strand, using a process of repeated heating and cooling with an enzyme or polymerase. By 1989 Jeffries was using PCR to amplify DNA samples for forensic profiling – ultimately helping in 1992 to confirm the identity, for German prosecutors, of the Nazi, Dr Josef Mengele, who had died in 1979 under another name.

Large scale PCR

PCR at the time, used an enzyme which could not withstand the rapid heating and cooling involved in the process. This made it cumbersome as it involved considerable human intervention.

In 1986 the team made a significant breakthrough when they isolated the heat resistant Taq polymerase which effectively

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removed the need for human intervention. Without a heat-resistant enzyme like Taq polymerase, PCR could not be used on a large scale as the process would have been too cumbersome.The following year the availability of a thermal cycler for regulating the temperature of a reaction made it possible to improve the PCR process once again. These developments have made PCR the simple and quick process that it is today.

PCR techniques have made it possible to amplify and analyse extremely small amounts of DNA samples. As already noted it has become an invaluable technique in forensics for the identification of criminals. However in conjunction with improved understanding around genetic disease, PCR has become fundamental to the early diagnosis of genetic diseases and the emergence of personalised medicine.

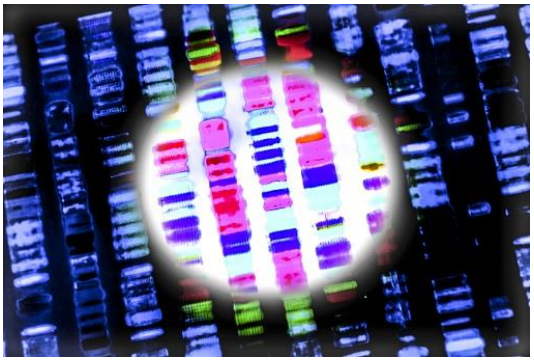
Mapping the human genome

In 1990 the Human Genome Project had been launched to better understand the hereditary instructions that make each of us unique. This global scientific research programme set out to work out the order (or sequence) of all the 3 billion DNA base pairs in the human genome. This was a major undertaking with the technology available and it wasn't until 2003 that the complete human genome sequence had been mapped, confirming that humans have approximately 20,000-25,000 genes. The ENCODE project then took up the challenge to identify and characterise all 25,000 genes in the human genome and to develop faster methods for sequencing DNA.

High-throughput genome sequencing

Improvements in genome sequencing chemistries and massively parallel sequencing, where many DNA fragments are read simultaneously and subsequently realigned and reassembled into long sequences, have driven down costs and the time to result. Now projects analysing many gigabits of sequence are possible at a reasonable cost.

The National Human Genome Research Institute describes (see figure 1) a profound outpacing of 'Moore's law' as a result of the transition from Sanger-based (dideoxy chain termination sequencing and capillary based instruments) to next generation DNA sequencing technologies.



As a result of the improved analytical methods being used, the cost to generate a high-quality draft whole human sequence has fallen to below $1,000. Ultra-fast sequencers designed for rapid analysis give results in as little as a few days.

The existence of a complete reference database for all 25,000 genes matched with high throughput and low-cost ways to conduct analysis is incredibly powerful. It has become a very significant tool that is readily available to

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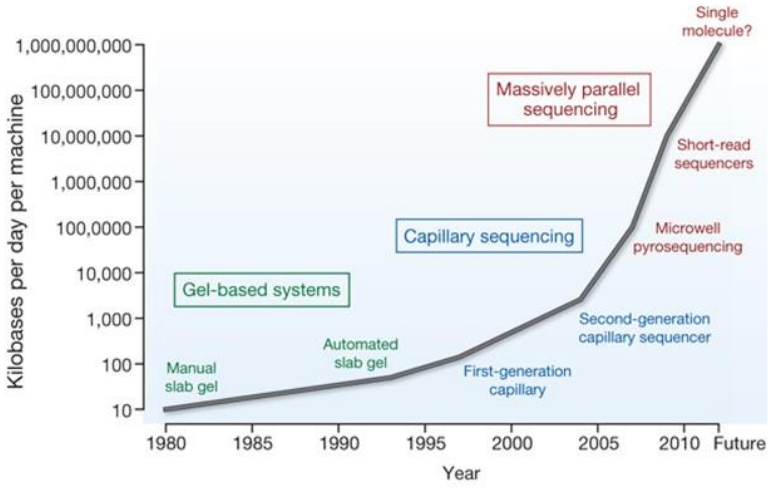
many researchers - enabling both fundamental research as well as the development of increasingly tailored approaches to diagnostics, treatments and patient care.

Improvements in the rate of DNA sequencing over the past 30 years and into the future.



MR Stratton *et al. Nature* **458**, 719-724 (2009) doi:10.1038/nature07943

nature

Genome sequencing, or Next Generation Sequencing (NGS), is only now beginning to transition from research labs to clinical labs. The applications are exciting and provide opportunities including:-

- Prenatal testing, using a maternal blood sample that contains fragments of the baby's DNA
- Newborn screening for rare and treatable conditions
- Diagnosis of suspected rare diseases
- Oncology and tumour profiling
- Pharmacogenomics- personalised therapeutic intervention

The emergence of pharmacogenomics

Pharmacogenomics is revolutionising healthcare by identifying candidate genes and polymorphisms and correlating these with subsequent therapies and clinical outcomes. The precision now available makes it possible to use an individual's genetic profile to guide decisions. It's no longer about one size fits all. Diagnostic testing focuses on the unique variation of the human genome and classifies individuals into sub-populations that differ in their susceptibility to a disease or their response to a specific treatment. This allows

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for increased tailoring. The emergence of pharmacogenomics uses an individual's genome to provide a more informed and tailored drug prescription. The ability to look at a patient on an individual basis will allow for more accurate diagnosis and specific treatment plans.

Biomarkers to personalisation

Genomic science allows researchers to understand, at a molecular level, the reasons why a protein fails to function, to discover and develop a medicine specifically to improve its function and to use the results of a genetic test to select the right patients for the drug. Clinical trials are becoming more tailored and are built around providing treatment for individuals with specific biomarkers. The knowledge which has come from the complete reference database of the Human Genome project (and commercial versions which has since been established) matched with the advances in next generation sequencing techniques and their falling costs, have created a real opportunity for developing precision drugs targeted at specific genetic mutations.

Precision medicine in action

Sagentia's scientists have developed a number of modular systems, based on PCR, to support multi-sample testing. As the biochemistry has matured this has been increasingly focused on reducing the time to result via extremely fast thermal cycling and simultaneous multi-colour optical measurements on each cycle. This technology is now a workhorse of the molecular testing laboratory, handling 100's of individual patient samples per day and is also available at the point of care as an easy to use device in which the user only needs to insert the sample into the fully automated test cartridge. Even with the advent of NGS, PCR remains extremely important as a method of amplifying small quantities of DNA for it remains faster and lower cost. Sagentia is also highly active in NGS - assisting with concepts for single molecule sequencing, base calling, algorithm sample preparation and technology review.

There are already obvious examples like the drug Vemurafenib, developed in 2011. BRAF is the human gene responsible for the production of a protein called B-Raf, which is involved in sending signals inside cells to direct cell growth. B-Raf has been shown to be mutated in some cancers. In 2011, Vemurafenib, a B-Raf protein inhibitor, and the companion BRAF V600E Mutation Test were approved for the treatment of late melanoma. As Vemurafenib only works in the treatment of patients whose cancer tests positive for the V600E BRAF mutation, the companion test helped to target the drug to just those patients who would respond positively to its use and help to target budgets and treatments to those it could most help. 60% of patients with melanoma have a BRAF mutation and around 90% of those are the BRAF V600E mutation.

Another high-profile example of how a pharmacogenomics intervention has helped to develop a highly targeted treatment is the medicine, Herceptin. Herceptin is an antibody

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that was developed after the discovery that the HER2 gene is amplified in 20-30% of early-stage breast cancers. The HER2 pathway promotes cell growth and division when it is functioning normally; however when it is overexpressed, cell growth accelerates beyond its normal limits. In cancer cells the HER2 protein can be expressed up to 100 times more than in normal cells (2 million versus 20,000 per cell). This overexpression leads to tumor formation.

In conclusion we can look to the Personalised Medicine Coalition who are excited about the future prospects in this area. Personalised medicine has the potential to change the way we think about, identify and manage health problems. As they state – it is already having an exciting impact on both clinical research and patient care and this impact will grow as our understanding and technologies improve.

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