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Guest Editorial

Genetic testing for inherited diseases – it is not just about diagnosis

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Just over two decades ago, in October 2004, the first complete sequence of the Human Genome was published (International Human Genome Sequencing Consortium, 2004). It was the culmination of a massive and expensive collaboration between 20 sequencing centres across the world, spanning more than a decade of work and at an estimated cost of over €2.5 billion. This first complete genome build made available the sequence of 92% of the 3 billion nucleotides that make up a human genome.

Fast forward 20 years, and advancements in technology – the development of high throughput sequencing and bioinformatics – have enabled us to fill in the missing 8% (Amaral *et al.*, 2023). More importantly, the advent of high throughput sequencing has made it possible to sequence an entire genome in a few hours and generate a list of genetic variants within a couple of days. All this for less than €1000 per genome. As more and more genomes are sequenced, we have also come to the realisation that there is huge variation between individuals, with any two unrelated people having around 5 million differences in their DNA sequence (The 1000 Genomes Project Consortium, 2015). These differences make us unique. These differences also underpin a vast number of genetic disorders. Unexpectedly this knowledge has ushered in a new era in medicine – the era of precision medicine.

Traditionally, testing for genetic mutations that caused disease was a targeted, sometimes lengthy, process that required knowledge of the mutation to be tested for. This was problematic for rare diseases, since the required knowledge was often not available. Modern diagnostics, including the search for new and unknown novel variants, takes a more holistic approach – sequencing the entire human genome and using bioinformatics to sift through the 5 million variants to get to the causative ones. This makes possible a definitive diagnosis for more patients, even those with the rarest of conditions (Ng *et al.*, 2010).

The principle behind second generation genome sequencing technologies is beautifully simple compared to the massive amount of data that it generates. DNA is obtained from any nucleated cell and broken down into small pieces. The DNA fragments are then ligated to short synthetic nucleotide sequences and bound to a solid support. Each fragment is read starting from the known synthetic nucleotide sequences. Since all fragments are immobilised, millions of them can be sequenced in parallel with fluorescence data collected in real time and stored in individual computer files. The sequence is then put together again, like a jigsaw puzzle, giving the individual's entire, continuous DNA sequence. A bioinformatic comparison to the standard reference sequence is finally used to identify DNA variations within the individual. The majority of the 5 million identified variants have no effect on health. Some may have subtle effects, where a variant influences risk for complex diseases such as diabetes or cardiovascular disease. A few variants will directly cause disease, mostly rare diseases.

'The right drug, at the right dose, at the right time' is the final aim of precision medicine, and knowledge of the exact DNA mutation causing the disease can at times determine treatment – thus personalising

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medicine. In this way, genomic data makes possible diagnostics, prognostics as well as targeted treatment. Cancer therapy is probably one of the clearest and best-known examples where patients with the same tumour may be given different targeted therapy based on the genetic mutation driving their tumour (Shuel, 2022). But the use of precision medicine extends beyond targeted cancer therapy. Locally we have used genetic analysis to determine that the type of phenylketonuria prevalent in the Maltese, is the rarer, atypical forms (Neville *et al.*, 2005) which do not respond well to solely a phenylalanine restricted diet but require additional neurotransmitter supplementation treatment with carbidopa and 5-hydroxytryptophan. Additionally, these conditions are far more prevalent locally than elsewhere (Farrugia *et al.*, 2007) and warrant their own screening programme which has been recently launched. As we continue to study the genetic basis of disease within the Maltese, we and others (Axiak *et al.*, 2023, Ciantar *et al.*, 2024) are finding that there are other conditions locally where genetic tests will not only offer a diagnostic result, but may also offer prognostic information and the possibility of targeted treatment with a concomitant improvement to quality of life, a reduced financial strain on medical services and better outcomes for our patients.

Moving forward, genomic testing will become an even more integral part of pathology, applicable not only to the study of inherited genetic diseases, but also infectious diseases as clearly illustrated by the expansion of molecular COVID-19 tests during the pandemic. Though it brings many benefits, genomics also brings with it several ethical and GDPR considerations. DNA sequences are shared with parents and siblings (and to a lesser extent with members of the extended family), and a genetic finding does not only belong to the individual, but to the family. When analysing a genome, other information not pertinent to the disease being studied may be uncovered. These incidental findings may impact a person's life in multiple ways. Thus, genomic medicine has huge potential, it is changing the way we carry out diagnostic tests and prescribe treatment, however, policies need to be put in place to safeguard both patients and clinicians such that the benefits may continue to outweigh the risks.

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