Genomic technology for patients

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The last five years has been an immensely exciting time for those doctors and medical students who love new technologies, or more importantly, who love what new technologies can do for patients. An expanding range of technological advances competes for our attention, such as: 3-D printing of cells to generate replacement tissues; augmented reality for clinical communication; health robots using artificial intelligence; cancer immunotherapy; and gene sequencing. Some of these new technologies are destined to be used by all practitioners in a specialty within the next five years. Other equally valuable technologies will remain research tools, used to build the evidence base for future medical practice, but are unlikely to be used directly by most doctors. Genomics and related 'omic technologies' sit in both camps, rapidly penetrating into the mainstream of primary and secondary care, while in parallel, transforming our knowledge of disease through research.

This article will argue that omic technologies are an advance that few doctors and medical students can ignore. It will describe the general landscape of omic technologies in New Zealand and overseas, then use two examples of omic technologies to illustrate the potential of this field: personal genomic testing; and polygenic risk scores. It will then discuss two challenges that are currently being addressed: the development of a genomically-literate health-care workforce; and issues of equity. Pertinent web sites and peer-reviewed references will be given for further reading.

What are omic technologies? Omic technologies generate masses of data to characterise pools of biological molecules in cells and tissues. Currently, the most widely used omic technology in medicine is genomics – the characterisation of DNA sequence. This is often divided into whole genome sequencing, exome sequencing (which sequences only that part of the human genome encoding proteins) and targeted panels (sequencing small subsets of the genome that are associated with disease). Other omic technologies are rapidly catching up to genomics, including: transcriptomics (RNA); proteomics (proteins); metabolomics (metabolites); lipidomics (lipids); and glycomics (carbohydrates). In all omic fields, the pace of technical advance is rapid and dramatic. This is best illustrated by genomics, where the shift from Sanger sequencing (sequencing one gene at a time) to massively parallel sequencing (capable of sequencing the whole genomes of many patients simultaneously) has been described as 'the most transformative technological advance in biomedical science since the development of the optical microscope'.[1,2]

So where have medical genomics and related technologies reached in Aotearoa New Zealand (NZ) and what is their future trajectory? Genomic tests using single genes or small sets of genes have been used in NZ for decades. Building on this expertise, NZ clinicians and research scientists have started to use next-generation sequencing in research studies where data can be fed back into patient care. Local examples include paediatric exome sequencing analysis to diagnose rare syndromes, and sequencing of cancers.[3,4] These studies are just a small part of a plethora of NZ medical-genomics initiatives, including Auckland's Genomics Into Medicine program and the national Genomics Aotearoa infrastructure.[5,6] In late 2018, a large-scale collaboration between a network of NZ general practitioners and an Australian genomics company was announced to undertake pharmacogenomics testing (analysis of genetic variants that affect medications) for NZ patients.[7]

However, despite this exciting activity, as a small nation with limited resources, our implementation of omic technologies in health care has lagged behind that of larger countries with similar health systems. For instance, as of December 2018, the United Kingdom (UK) Genomics England organisation had sequenced 100,000 genomes through its 13 Genomic Medicine Centres, facilitated by carefully governed partnerships with researchers and industry.[8] In Australia, the 2018 government budget provided a AU$500,000,000 investment for genomics to save or transform the lives of 200,000 Australians over ten years.[9] This seeded Australian Genomics, an alliance that brings together 80 clinical and research organisations. Investments in genomics for health and well-being are being made in many other Western nations, complementing large health data research studies such as 'All of US' in the United States of America.

An interesting example of medical genomics is Personal Genomic Testing (PGT). PGT involves individuals ordering their own genomic analysis online and is a rapidly growing industry. PGT is sometimes perceived as a route to 'precision health' – optimising the wellness of already healthy people. Although individuals using PGT are sometimes perceived as consumers of health care rather than patients, PGT is rapidly evolving from a purely direct-to-consumer model, into a model where health-care providers, directed by their patients, are intimately involved. PGT can generate a range of information, including: ancestry; predicted traits related to fitness and nutrition; pharmacogenomics; and carrier status for inherited disease.[10] As a result, medical practitioners play a difficult role in PGT, since only a subset of this information has a clear medical indication, a scientific evidence base, and rigorous regulation.[11] The scientific evidence base of some

other information included in these tests is either still emerging or downright absent. This complexity makes it difficult for individuals to interpret their own PGT results using readily available, but sometimes conflicting, web tools and blogs. The bandwidth of secondary-care genetic counsellors and clinical geneticists to assist with PGT impetration, and their knowledge about the ever-changing smorgasbord of PGT available, is also limited. Therefore, primary-care doctors and nurses will increasingly be called upon to order and interpret PGT. This will require them to both learn new material, and use their existing skills and experience to communicate a nuanced interpretation of the range of information provided by these tests in the context of the person in front of them and their medical history. This is a current reality, not just a future possibility. In a 2016–2017 survey of more than 2800 Australians, ~10% had undertaken PGT; of these ~60% would seek help from their general practitioner for interpretation of medical aspects of the test results. Even more challenging for general practice, ~ 25% would seek help from their general practitioner to interpret non-medical test information such as ancestry and traits.[12]

Another example of medical genomic technologies is Polygenic Risk Scores (PRS). PRS involve a set of tens to hundreds of single nucleotide variants in an individual's genome that is being sequenced, which are then summarised statistically.[13] PRS are emerging as important predictive tools to guide screening programs, clinical interventions, and life planning.[14] They are often more predictive of a disease than any single genetic variant is alone. This is in line with large-scale genome-wide association studies, which frequently identify hundreds of individually-weak genetic variants that interact synergistically to strongly influence the incidence or outcome of a disease. PRS have been used for everything from cardiovascular risk prediction to prediction of breast cancer risk and sub-type.[15,16] However, with current methods, the 'uncertainty' in PRS predictions at the level of an individual person can make them difficult to interpret.[14] In addition, many PRS have been derived from limited populations, so biases and inaccuracies can be introduced when they are then applied to populations with different genetic characteristics than those in which they were generated.[17] Since most of these limitations appear resolvable, especially if PRS are intelligently combined with existing clinical data, PRS are a technology likely to reach further into both primary and secondary care over the next five years.

The largest challenge we face today is generating a genomically-literate health care workforce and genomically-literate patients. The 2016 UK Chief Medical Officer's report stated 'modern genomic science has evolved into a new concept of the "clinical team" which now includes: diagnostic staff in laboratories and imaging; computer scientists; statisticians; (bio)informaticians'.[18] A major challenge seems to be clinicians acquiring the data science skills needed to integrate genomic information with health records, pathology tests, and their traditional clinical acumen. However, this integration is essential, since medical genomics is only effective when driven by, and interpreted alongside, patient-specific clinical information.[1] For nurses, general practitioners, pathologists, physicians, and surgeons to undertake this complex integration, significant capability development is often needed as part of their continuing medical education. For instance, in February 2019, Professor Eric Topol's UK National Health Service review noted that, 'within 20 years, 90% of all jobs in the NHS will require some element of digital skills', and that 'all staff will need digital and genomics literacy'.[19]

The rate with which medical genomics is developing has forced us to address issues in equity of access, genomic data governance, data security, and medical ethics, which have not previously been resolved.[20] For instance, current genomic technologies may serve some ethnicities much better than others, due to disparities in the inclusion of different ethnicities in the genomic databases used to interpret gene sequence data.[21] This has encouraged a group of NZ genomic scientists and clinicians to initiate a NZ 'variome' project, which will be co-governed by Māori and Pacific People in order to define the distribution of genomic features across NZers.[22] An additional challenge recently in the news is the ethical issues about genomically-directed technologies for genetic repair in utero using CRISPR-Cas9 and related methods.[22] This has recently resulted in a World Health Organisation panel proposing an international global registry for all CRISPR-Cas9 experiments in humans.[23]

This article has summarised the potential of medical genomics and their challenges. Right back in 2016, Dame Sally Davies, the UK's Chief Medical Officer, said in her annual report 'Genomics is not tomorrow. It's here today'.[18] However, it is clear that omics technologies have reached the clinic in some places earlier than in others. A historical quotation from the writer William Gibson aptly describes the current state of omics in NZ health care: 'The future is already here – it's just not very evenly distributed'.[24] In NZ, despite lagging behind some of our large international partners, we can look forward to an exciting future in medical genomics. Yet, in among this excitement, we need to be vigilant that the genomics we do in NZ has a firm evidence base, that it includes appropriate levels of co-governance with Māori, and that we add data science to our list of required skills.

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