Genetics and genomics in healthcare: the future is now

'*Life can only be understood backwards; but it must be lived forwards'.*

— Søren Kierkegaard, *Journalen IV A 164*, 1843

'*The future depends on what you do today'.*

— Mahatma Gandhi, *Autobiography: The Story of My Experiments with Truth*, 1983

It is hard to imagine medical practice without the expansive knowledge of genetics and genomics that has been accumulated over decades.[1] While personalised healthcare has been deemed to be the ultimate nirvana of modern medicine, its origin dates back to 1901, when Karl Landsteiner of the University of Vienna discovered ABO blood typing to explain why some blood transfusions were successful while others were deadly.[2] In today's era, ABO blood type represents one part of each individual's medical identity. Indeed, it did not take long after the discovery of the double helix by Watson, Crick and Franklin in the early 1950s to highlight that DNA is the blueprint of life.[3] The central dogma of molecular biology then ensued in 1958, to delineate the flow of genetic information from DNA to RNA to protein.[4] What followed is a burst of advancements that may have been considered mere impossibilities by dwellers of our past times. Today, it is not only possible to affordably sequence the entirety of the human genome within a few days, but it is also possible to edit the genome to 'fix' genetic errors that cause debilitating human diseases such as sickle cell anaemia and β-thalassemia.[5]

One paradigm that progressed over the past decade is how we view and manage hereditary disorders, with heritable cancer leading the way. One predisposition gene to one inherited syndrome was the rule for many years until germline *RET* mutations were found to predispose to multiple endocrine neoplasia type 2 and to the seemingly unrelated Hirschsprung disease based on mutation effect (gain-of-function versus loss-of-function, respectively).[6,7] In 1997, germline mutations in the tumour suppressor gene *PTEN* were shown to predispose to Cowden syndrome, a hereditary cancer predisposition disorder.[8,9] In 2005, emanating from the clinical observation that Cowden families had an overrepresentation of children with autism spectrum disorder (ASD), a systematic study confirmed that germline *PTEN* mutations cause a subset of ASD with macrocephaly.[10] Over the last two decades, efforts from various groups around the world have shown that *PTEN* is one of the most common causes of ASD at large, one of the most highly somatically mutated genes in sporadic cancers and one of the most versatile and well-studied proteins in humans.[11,12] To facilitate medical management, *PTEN* hamartoma tumour syndrome (PHTS) was coined to represent the molecular diagnosis of harbouring a germline *PTEN* mutation, regardless of phenotype, because medical management is informed by a specific gene mutated.[13] With the discovery of *PTEN*-enabled gene-specific cancer risks and tailored medical management, it remains impossible to predict whether any *individual* (versus group) PHTS patient will or will not have cancer and/or ASD.[14] Hence, with the increased depth and breadth of knowledge comes more unanswered questions. This is pertinent not only to *PTEN*, but also to the vast majority of genes associated with hereditary conditions.[15] These themes are echoed in the vast majority of review articles and case vignettes presented in this issue.

As a practising medical geneticist for the past 25 + years (C.E.), I appreciate how far we have come in this realm and often reflect on where we are heading to. As predicted more than a decade ago,[1] personalised healthcare is closest to reality as it has ever been. In the next few decades, I envision that the genetic and genomic arenas will continue to grow at an unprecedented pace, while importantly, amalgamating interactions between physicians, scientists, genetic counsellors and clinician-scientists to put the clinical context together with content. Telegenetics has enabled greater access to genetic counselling services, and I predict that telemedicine will continue to constitute a major component of medical care, with facilitated and more accessibility globally, beyond borders. Chatbots will facilitate such interactions by presenting genetics education typically given by a genetic counsellor, where demand far outstrips supply, and triage individuals based on disease risk profiles. Massive amounts of genetic and genomic data will continue to be produced. Ancestry will play a significant role in understanding disease aetiology and tenets of graceful ageing, guiding more precise risk stratification and medical management. Additionally, with the ability to easily and affordably track personal vital signs in real-time and longitudinally, these deep phenotyping efforts will likely be integrated with each patient's electronic medical record (EMR).[16] Pharmacogenomics and genomics-informed targeted therapies will guide tailored drug types and dosing before regimen initiation to ensure a high therapeutic index. Beyond utilising the host genome for precision care, we are now entering the era where gut and organ-specific microbiome studies not only can forecast and predict outcomes or a disease state and responses to therapy,[17-20] but in the future, may direct specific probiotics aimed at correcting dysbiosis.[21] Inevitably, every person will have their whole genome sequenced and embedded in their EMR. Beyond the ACMG set of clinically actionable

genes, having a sequenced genome embedded in an EMR will be optimally useful only if every variant can be interpreted with the clinical context (i.e. outcome), and that management crystal clear for each actionable variant. Variant interpretation will continue to be a challenge but will be facilitated by global standardisation efforts and massively parallel variant functionalisation. However, this worthy challenge forecasts a dynamic and rapid change in the way genetic and genomic data are interpreted, particularly to mitigate the ever-rising number of variants of uncertain significance. As such, family history will take on more prominence because personal and family phenotypes provide clinical context to genomic content, guiding management and the earliest preventative measures.

Intriguingly, the picture we paint might not seem as foreign for newly minted medical geneticists and genomicists, particularly in the developed world. But to thrust medical genetics and genomics forward, it will be vital to ensure accessibility and impact regardless of geographic location. While national and international consortia have been tireless in ensuring inclusivity of all ancestries in genetic and genomic studies, it will be equally important to sustain these efforts if we are to truly uncover the most comprehensive aetiologies of hereditary diseases. Undoubtedly, we anticipate that the upcoming few decades will witness the growth of computational technologies to catch up with the massive amounts of data, not only for research purposes, but also for practical patient care. Importantly, all these rapid medical advancements in just one field, human genetics and genomics, call for the need for further specialisation (e.g. clinical cancer genetics, cardiovascular genetics, neurodevelopmental genetics) and wide integration of specialised genetic counselling services as a backbone for such clinics. Because the patient lies at the core of all these efforts, formal training in the practice of specialty genetic and genomic medicine of the next generation will be of paramount importance. Indeed, the future is now, and it is our duty and responsibility to ensure beneficial outcomes for our patients and their families.

'*The doctor of the future will give no medicine, but will interest his (sic) patient in the care of the human frame, in diet and in the cause and prevention of disease'.*

— Thomas A. Edison (1847–1931)

'*The future belongs to those who believe in the beauty of their dreams'.*

— Eleanor Roosevelt, 4 July 1957

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