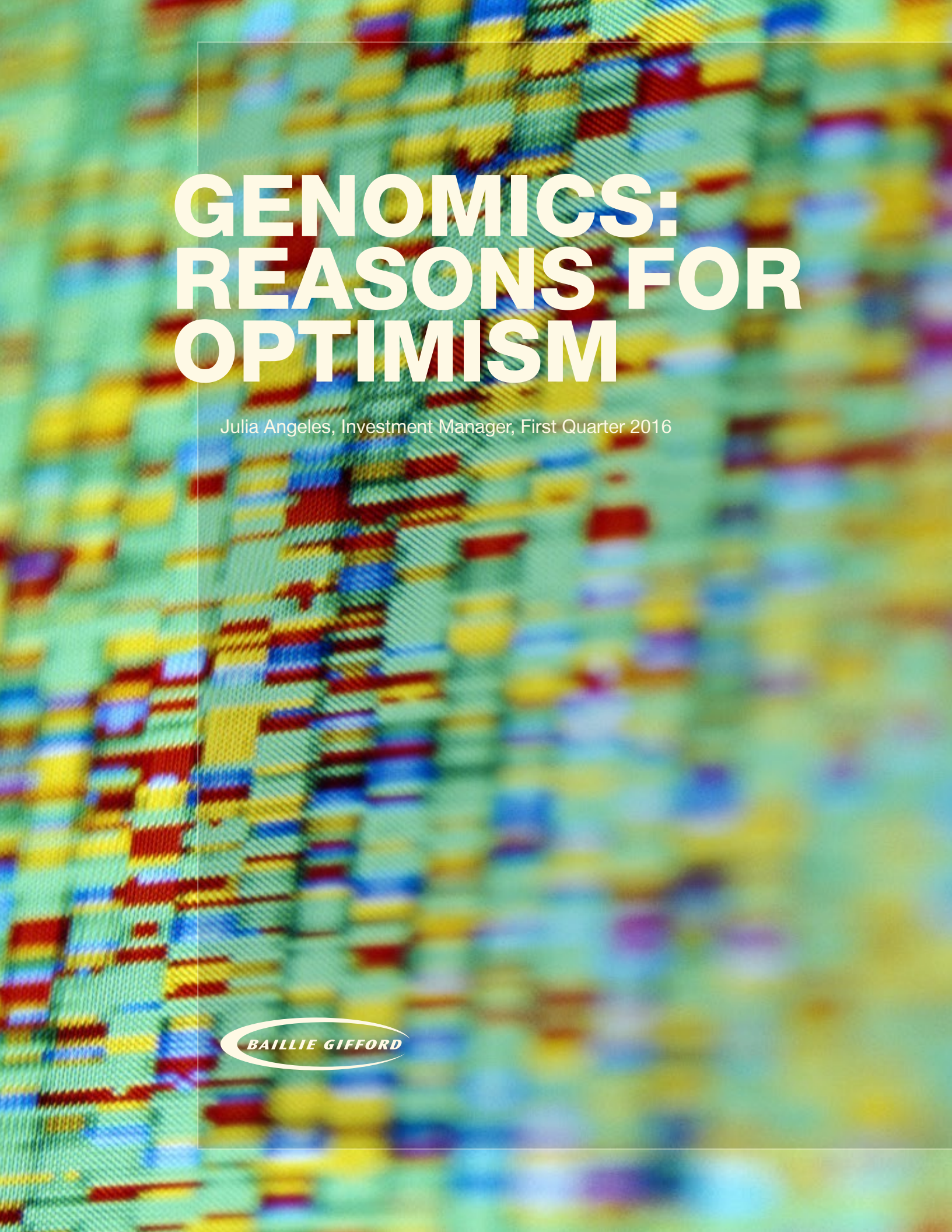

GENOMICS: REASONS FOR OPTIMISM

Julia Angeles, Investment Manager, First Quarter 2016

BAILLIE GIFFORD

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JULIA ANGELES

Investment Manager

Julia has a particular interest in healthcare. Julia's core contention is that over the next 10 years healthcare systems around the world will experience a monumental change. She believes that we will witness a move away from traditional to a world where prevention and cure will become an integral part of healthcare.

Julia holds a PhD in Economics from the University of Aarhus, Denmark and speaks fluent Russian and Danish. Before joining Baillie Gifford in April 2008, Julia worked as a Management Consultant at McKinsey & Company advising firms in Denmark, Russia and Hungary. Julia has been part of different global and regional teams within Baillie Gifford and is currently a member of the EAFE Alpha Portfolio Construction Group and the Positive Change Portfolio Construction Group.

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Cover Image: Computer screen display showing the coloured bands of an autoradiogram showing genetic sequences. © Alfred Pasieka/Science Photo Library.

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GENOMICS: REASONS FOR OPTIMISM

BY JULIA ANGELES

Human biology is complex. Each of us is made up of 100 trillion cells. The majority of these cells don't belong directly to us but to micro-organisms that live inside the gut and interact with the immune system. Our DNA consists of 3 billion sub-units (the bases A, T, C and G) and we have approximately 20,000 genes that are responsible for coding more than 100,000 proteins. Clearly, human biology is a system of large numbers.

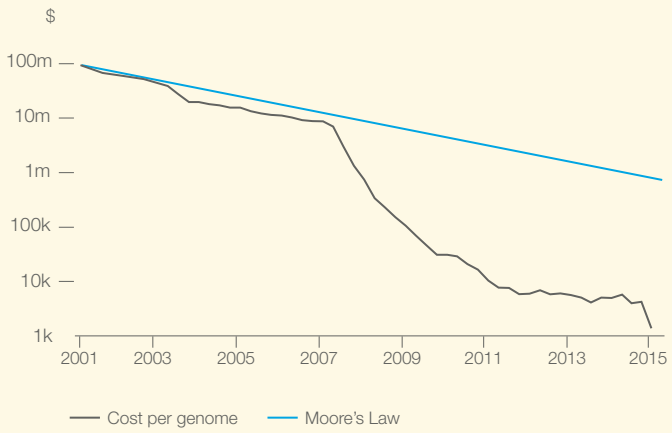
Given this complexity, it is hardly surprising that healthcare professionals have difficulties in delivering a precise diagnosis and addressing the underlying causes of diseases. In fact, we might only understand a small fraction of how the human body works.

This may be about to change. I think that over the next five to ten years we will be closing our knowledge gap and developing therapies that address the underlying causes of diseases. The reason for such optimism is a new tool box now available to researchers and scientists. One of the instruments in this tool box is genome sequencing. Whole Genome Sequencing (WGS) is a process that determines the identity of 3 billion sub-units that compose the human genome.

A DNA sequencer being used to create automated samples in a biology lab.

It is no exaggeration to say that we are experiencing a genomic revolution. The cost of WGS has been reduced by around 1 million times compared to the first human genome project that took place more than two decades ago. And genomics is already benefiting patients.

Cost per Genome



Source: National Human Genome Research Institute.

Let us consider, for example, rare diseases. These diseases remain unmet needs as some of them are found in no more than a few thousand patients and therefore receive little attention from the research community and the pharmaceuticals industry. However, some rare diseases occur in as many as 200,000 people. In fact there are more than 6,000 known rare diseases that affect more than 300 million people globally.

Most rare diseases have a genetic source and the WGS is increasingly being used for the diagnosis. This already has a profound impact on many patients and their carers in the form of pre-emptive and targeted treatment and offers the psychological benefit derived from knowing what is wrong and how to approach the condition.

Cancer is another area where genomics can significantly affect the diagnosis and treatment of the disease. This is because cancer is a genomic disease where genetic mutations lead to uncontrolled cell divisions. For many decades we were fighting cancer blindly without understanding its biological nature.

Thanks to genomics we are not blind any more. During the past 30 years, scientists have uncovered more than 100 genes that drive cancer and, thanks to new screening technologies, the pace of innovation is increasing. For example, just one recent study increased the catalogue of cancer genes by 25%. These discoveries have already transformed therapeutic development. There are more than 800 different anti-cancer drugs in clinical development today. Many of these drugs are only relevant for a sub-group of patients that have specific cancer mutations and genomics can help to identify these.

Precise diagnostics achieved with the help of genomic testing are already saving many lives and making an impact on patients' well-being in the case of both rare diseases and cancer. There is still a lot to do, especially in the bulk of complex diseases such as Alzheimer's and Type 1 diabetes, where both genomics and environmental factors contribute to diseases. However, the progress made so far is very encouraging and gives grounds for hope.

The genome sequencing technology is also proving to be a very useful tool in exploring the immense world of micro-organisms that live inside and outside the human body. For example, a large genetic study related to the human gut led scientists to conclude that obesity is a heterogeneous condition and some obese people have a benign prognosis whereas others progress to co-morbidities such as Type 2 diabetes. According to the study, the difference in the risk profile can be explained by the difference in the microbial profile.

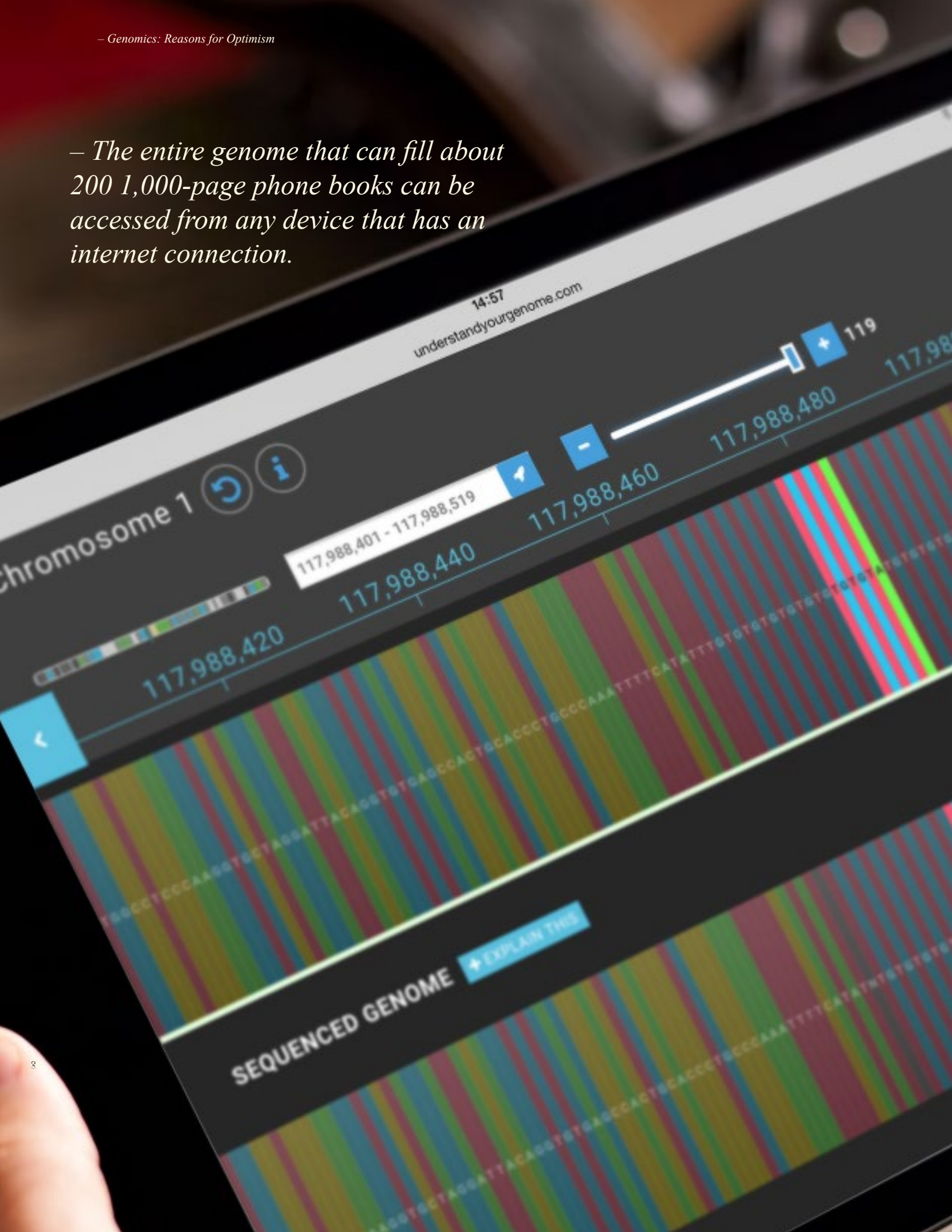
Another project is related to the analysis of New York City's subway system surfaces. Interestingly, 48% of the genetic material of screened micro-organisms collected from the subway did not match anything yet identified. What role might these micro-organisms be playing in human health? We still don't know but I suspect this is only a matter of time.

While genomics has already proved to be an important tool for learning about different diseases, a more challenging question is whether genomic knowledge can be of any benefit to healthy people. There is a big debate in the scientific and public community about what can be gained by sequencing healthy people. On one side there are strong proponents who believe in the preventive healthcare system where genomics would play an important role. On the other side there are sceptics that see no clinical gains accruing from sequencing healthy people.

Subway Station, New York City.

– 48% of the genetic material of screened micro-organisms collected from the subway did not match anything yet identified.

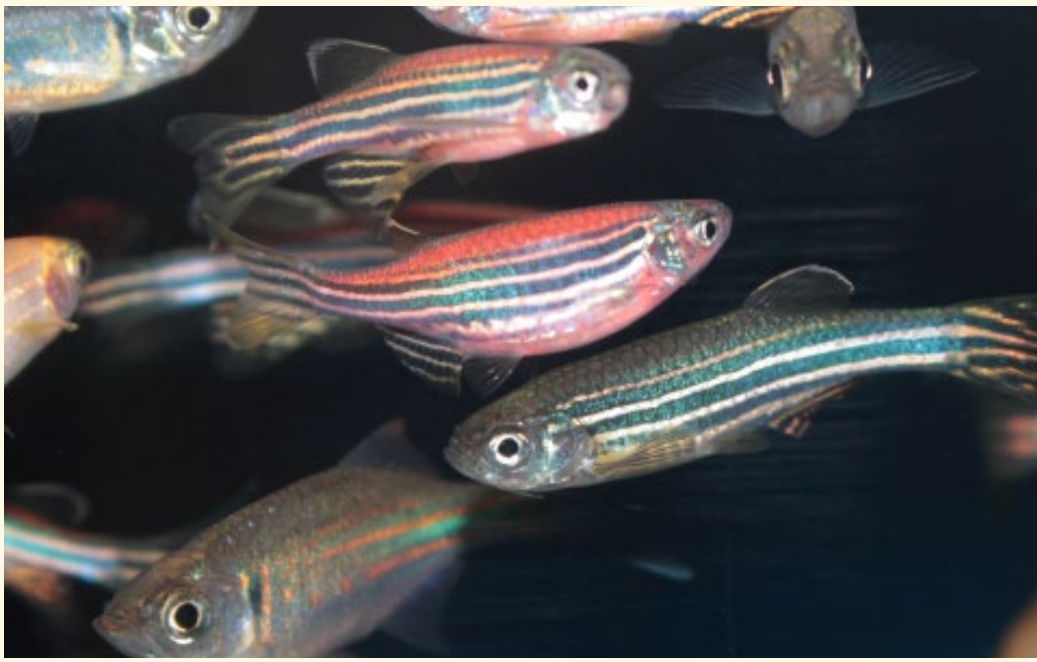
– The entire genome that can fill about 200 1,000-page phone books can be accessed from any device that has an internet connection.



In order to get closer to the debate and educate myself, I decided to join an Understand Your Genome (UYG) symposium. UYG is an educational movement that engages people to learn about genome sequencing with the help of experts and thought leaders in the field. These symposia take place globally and are organised by Illumina, a world leader in gene sequencing technology.

The idea of joining the UYG was also intriguing because there was an option to do your own genome sequencing as part of the programme. I decided to try because I thought that the access to my own genomic data would be helpful for building an understanding of the current opportunities and limitations of genome sequencing and also in allowing me to follow future progress more closely.

I didn't really know what to expect, whether to worry or to be excited. In the end, curiosity took over concerns and now, looking back, I think it was worthwhile. What surprised me most was how something so complex and overwhelming could be made accessible to a general audience in a simple and intuitive way. The entire genome that can fill about 200 1,000-page phone books can be accessed from any device that has an internet connection. Exploring your genome while waiting for a bus is as simple as playing a game. It is possible to navigate across the entire genome at different levels of granularity, ranging from a single base pair to genes and chromosomes.



The zebra fish is a popular model organism in biological research as its genome is fully sequenced.

There were two things that I found particularly useful in this test. The first was the screen to establish whether I am a carrier of high penetrance genes' mutations that could lead to conditions such as cystic fibrosis or hereditary cancers. Many of these disorders cannot currently be treated or prevented. However, this might change in the future. For example, in the case of cancer and cardiovascular related syndromes, early interventions could potentially improve patients' outcomes.

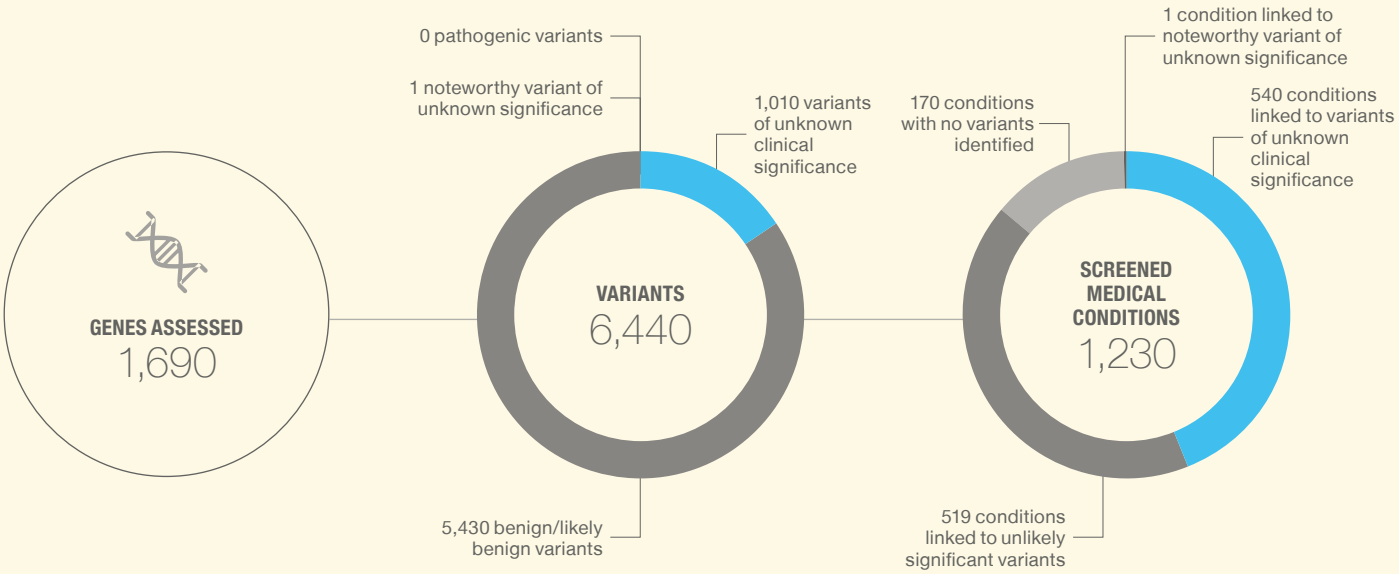
Gene editing technologies are also rapidly progressing from being research tools to technologies that might be used for the treatment of many genetic diseases. CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats) is the unwieldy name given to the latest ground-breaking genome editing technology that, thanks to its lower cost, simplicity and effectiveness is winning popularity among scientists and biotech start-ups. CRISPR not only keeps the promise to cure genetic rare diseases, but also to become an effective tool to expand our knowledge of genes' functions in health and diseases. For example, in order to study a gene's function, scientists can use CRISPR to knock down a gene in an animal model and then observe what it means for biological processes. The zebra fish is becoming a popular animal model, because about 70% of its genes have human counterparts, it propagates quickly and its embryos are transparent, making them easily accessible for research. These small freshwater species are already providing valuable insights into human biology and diseases.

The second useful learning for me was related to pharmacogenetic tests that assess the correlation between an individual's genetic makeup and the response to a given medication. This knowledge should lead to more accurate drug dosing and to the prediction of adverse reactions. For example, if I am ever prescribed an anticoagulant drug, Warfarin, I would tell my doctor to take into account that I have a low sensitivity to the drug. As a result, she/he can adjust the dosage accordingly. There is still a lack of evidence for clinical benefits of applying pharmacogenetic tests. However, I think it is a question of time before we start using them more widely.

I was also surprised to learn that we already know 4,000-5,000 disease associated genes. When the human genome project started in the 90s, we understood only a few dozen diseases. This is a remarkable rate of progress. However, I also realised how much we still need to learn. For example, my genome test provided clinical interpretation for 1,690 genes associated with 1,230 conditions. This test detected DNA's insertions/deletions and DNA's single base substitutions e.g. T is substituted by C. Out of the total of around 6,440 detected variants, it was not possible to draw any conclusions for 16%. This is because either little or nothing has been reported on these variants or because there is conflicting evidence about the variants' effects. As a result, it was not possible to draw any conclusions for 44% of assessed conditions that are linked to these variants of unknown clinical significance.

I also learned that the assessment of whether a certain variant plays a significant role in a disease is far from being a simple process. The interpretation of a variant depends on the methodology and the availability of research data related to the variant. Encouragingly, great efforts are being made to standardise the assessment process. Different data sharing initiatives should also improve the quality of interpretation in the future.

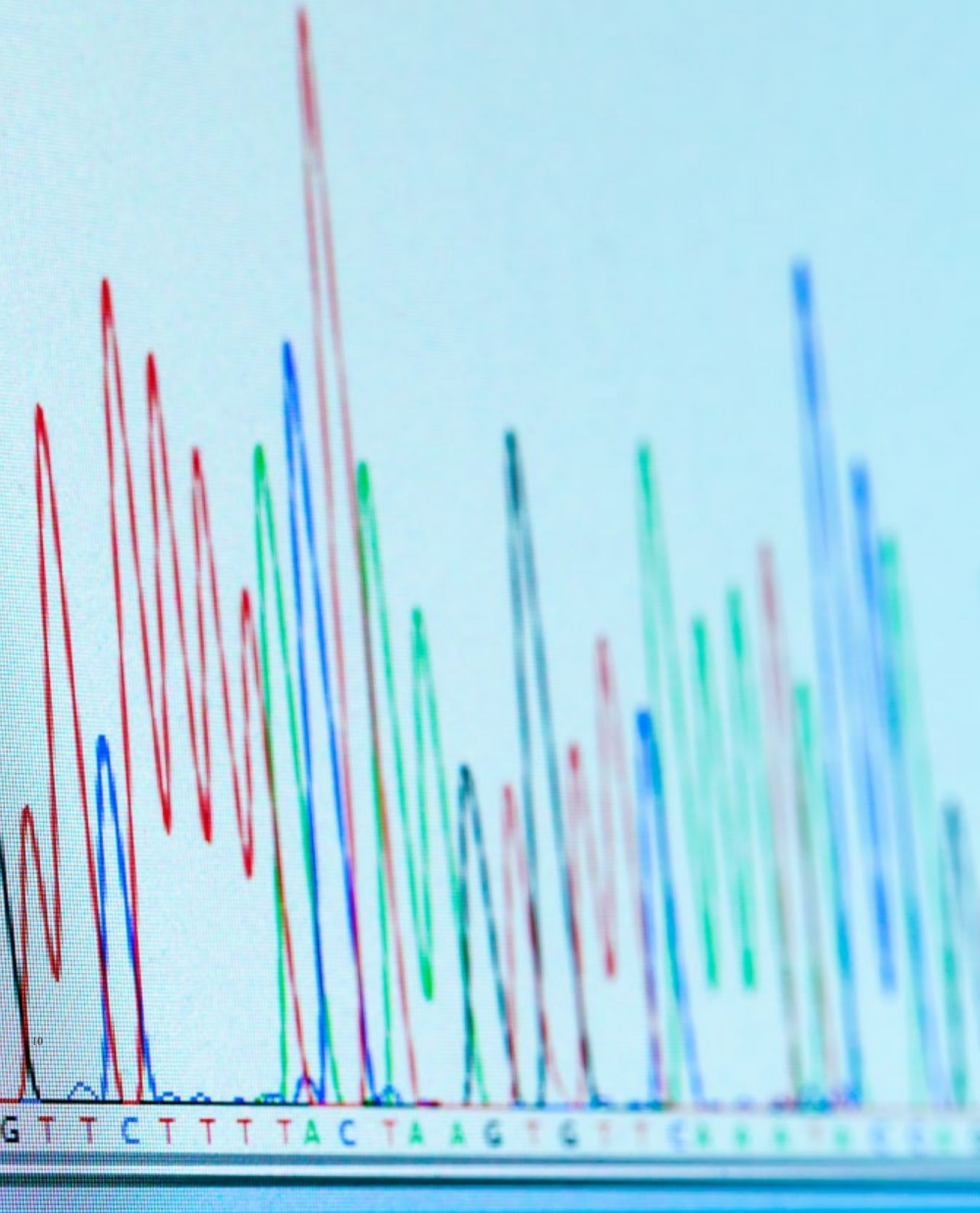
There was a general agreement among the participants in the UYG symposium that genome sequencing of healthy people is still far from being a clinically relevant test. We need to learn about the clinical significance of many more variants. We also need to assess how the information delivered by the test will be used in the clinic and whether the actions taken by doctors would be beneficial for patients. However, there was also an agreement that we are learning fast and in five years the situation might be very different from now.



Numbers may not sum due to rounding.

While genomics is already making a large impact on the lives of people with rare diseases and cancer, it is very important to remember that this is only one of the important tools that will help us to resolve the mystery of human biology. In the search for answers, scientists are building complex models that, besides genomics, incorporate interactions between proteins and external factors that can influence a gene's expression. By leveraging on the increasing computing power and smart algorithms, the hope is that these models will get us closer to understanding human biology and the underlying causes of complex diseases. This knowledge should eventually lead to effective therapies if not cures.

There are reasons to be optimistic.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