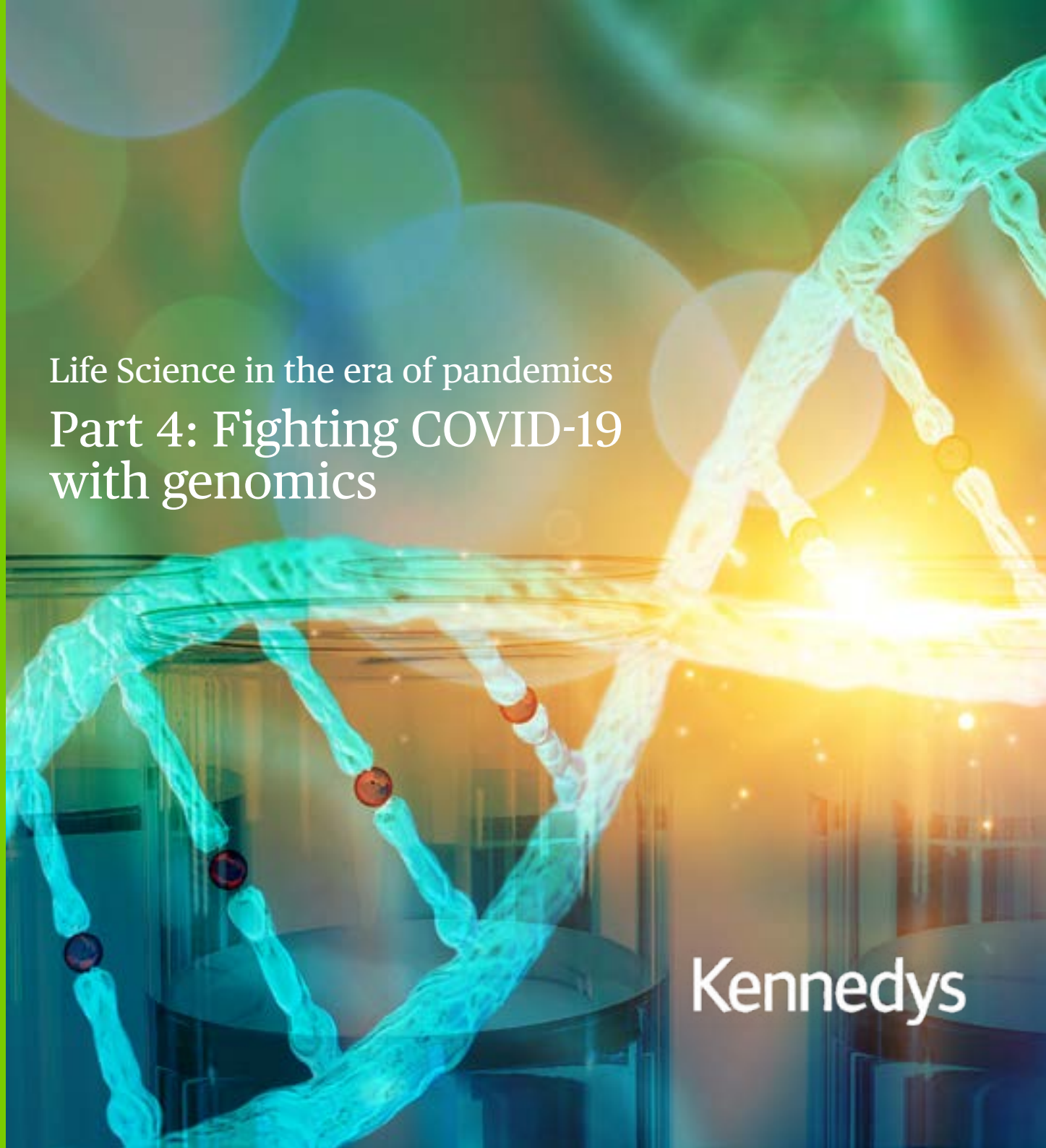


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Life Science in the era of pandemics
Part 4: Fighting COVID-19
with genomics

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Fighting COVID-19 with genomics

“Starting with the sharing of the first sequence in mid-January, we now have over 160,000 COVID-19 sequences shared on open-access platforms,” says Keith Gallois, Senior Risk Engineer, Chubb. The purpose of this continued, prolific sequencing of the virus’s genome is to track different strains.

“You’re analysing, through genomics, where strains from different jurisdictions fit within the global phylogenetic tree,” says Karishma Paroha, Senior Associate, Kennedys. This kind of analysis has identified a strain of coronavirus that started in Spanish farm workers in the summer and spread through Europe as holidaymakers returned from the country. By September that one strain of the virus accounted for the majority of new COVID-19 cases in the UK.

Understanding how the virus is spreading around the world in real time enables governments to take action to limit its transmission, such as requiring travellers to self-isolate. Frequent genome sequencing also means mutations to the virus that might render vaccines ineffective can be detected early and hopefully eliminated.

The genomic tools available to us now represent a new playbook when it comes to tackling pandemics. “It’s a whole different ball game from what we saw with SARS. All of the work we’ve done over the past 10 years with genomics has been utilised to understand what the virus looks like and how it attacks the body, and therefore come up with a mechanism to attack it back,” explains Alex Forrest, Head of Life Sciences - Overseas General, Chubb.

When it comes to attacking the virus, the Pfizer and Moderna vaccines are the first in a new generation

Advances in genomics are turbocharging the global response to the COVID-19 pandemic and continuing to redefine how we understand healthcare

When the Black Death seized the world in the Middle Ages, the words did not exist to describe what was killing millions of people. When COVID-19 was identified as a pandemic risk in the first few days of 2020, Chinese scientists peered deep inside the virus and sequenced its genome, reading the genetic ‘instruction manual’ for how it is built.

That genome sequence was shared with the international community and researchers quickly brought genomics - the study of an organism’s full set of genes and how they function - to bear on the virus.

Contributors



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What is a genome?

A genome is a complete list of instructions to make an organism

In humans, those instructions are stored in every cell in the body, within 23 chromosomes, which are made up of 20,000 genes, in turn made up of more than three billion letters of DNA. All of the DNA within a human cell makes up a genome

Only 0.2% of an individual's genome is different from that of every other human being. In that tiny difference is the potential to predict, prevent, diagnose and treat disease

Sources:
www.yourgenome.org
www.genomicseducation.hee.nhs.uk
www.genome.gov



A **gene** is a section of DNA. Some genes contain instructions for our individual physical characteristics, others influence our risk of developing disease

The instructions within each gene can be read through its genetic code, which is made up of four base letters of DNA - A, C, G and T - each representing a different chemical

16%

of Europeans carry genes putting them at higher risk of COVID-19-related respiratory failure

- ▶ harness genomics to train the human immune system against COVID-19 using ‘mRNA’ molecules. Conventional vaccines are made from viruses that are grown and then weakened in a laboratory in a process that can take months. By contrast, the mRNA vaccines can be developed in a matter of weeks from DNA templates without the need to grow the virus, dramatically speeding up the process of delivering a vaccine.

As the pandemic wears on and more data becomes available, genomic research is also shedding light on why some people are at a higher risk of severe COVID-19 than others. One study found that a gene cluster inherited from Neanderthals and carried by around 50% of people in south Asia and 16% of people in Europe was a major risk factor in respiratory failure in COVID-19 patients.

A much bigger picture

The role genomics is playing during the coronavirus pandemic provides a window on to this relatively new field and how it is transforming healthcare. As we have seen during the pandemic, genomics allows us to understand disease and the human body in a new level of detail. But what we have seen through the lens of COVID-19 just scratches the surface of genomics, which is leading us towards predictive and personalised healthcare.

“Having produced the first draft sequence of the human genome about 20 years ago, we’re getting to the real wide-scale practical use of that understanding,” says Vicki D’Silva, UK & Ireland Life Science Manager, Chubb. “Cancer is at the forefront

of the practical application of genomics. Right now the focus is optimising different types of cancer treatment on the individual genomes of those cancer cells, but it will definitely lead into other areas.

“The first lightning rod for real change was the BRCA1 gene for breast cancer,” explains D’Silva. The BRCA1 gene was linked to breast and ovarian cancer back in 1994 and women are now able to take a test that determines whether they have a faulty copy of the gene, which plays a part in cell repair in the body, and what risk they have of developing cancer.

This is an example of genomics unravelling the roots of disease and defining it more accurately; in this case a single-gene disorder, where one faulty gene is associated with a cancer. It is also an example of how genomics can be used to predict disease, which opens the door to preventative measures even before symptoms appear. Indeed, actor Angelina Jolie made BRCA1 famous in 2013 when she announced that she had undergone a double mastectomy as a preventative measure following a test that indicated she had an 87% risk of developing breast cancer.

Revolutionising treatment

BRCA1 is also an example of genomics influencing treatment, as scientists have used their understanding of the gene to create a targeted therapy - PARP inhibitors - that exploit the same fault in cancer cells, preventing them from repairing themselves.

Computing power and a dramatic reduction in the cost of full genome sequencing has been opening up



- genomics as an area of medical research. And that research has been transforming treatment in oncology, with a growing list of drugs that target specific gene mutations within cancers.

Paroha highlights Herceptin as one example. The drug blocks the effects of the gene HER2, which is found in high levels in some types of breast, oesophageal and stomach cancer. By diagnosing the patients with HER2-positive cancers, doctors can prescribe Herceptin, skipping straight to the most effective drug rather than going through several lines of treatment before finding the best one.

There are countless impressive examples of targeted medicines saving lives. But at the cutting edge of therapeutic genomics is 'gene therapy', an experimental technique whereby faulty genes are replaced or turned off to help the body fight disease.

Pharmacogenomics - the study of how genes affect a person's response to drugs - is also making medicine more targeted, enabling more tailored dosing or selection of drugs. "Pharmacogenomics is not only about trying to match patients with medications, but also trying to reduce the likelihood of adverse drug reactions," explains Paroha.

Studying the impact of the environment is also crucial to unlocking the full power of genomics. "It's about understanding what your body needs and how it interacts with the environment around you - either your ability to process carcinogens because your body is great at dealing with oxidative stress or how much sleep you need," says D'Silva, referring to the discovery

of two genes linked to people who need less sleep than most. "Those genes can make a human require only about four hours of sleep and that's a recent discovery in the last few years. On the flip side of that there are going to be genes that mean people need 10 hours' sleep. And for you to recognise that as a human is important - for you to understand how far you are pushing your body outside of what its normal range is."

As well as more serious health concerns, genomics is being used to analyse how our bodies might respond to different diets, exercises and lifestyles. "We've insured companies where you can send in a sample and they will write a genomic test for indicators that will tell you whether you should do cardio all the time, or strength training because your body responds best to that kind of exercise," says Forrest.

Together, these advances are taking us towards more personalised medicine, with a bigger role for prediction and therefore prevention, more accurate diagnosis of conditions, and targeted treatments dosed appropriately to our biochemistry.

Where next?

The application of genomics in healthcare may have started in oncology, but it is expanding into many other areas as the cost of sequencing continues to plummet and researchers gather ever more data, uncovering genetic markers for all kinds of different diseases.

"We are now in a world where genome sequencing of mass populations is starting to come to the fore. In the United Kingdom, whole genome sequencing is already





What is CRISPR?

A gene editing technique that allows us to add, remove or alter DNA and therefore change the characteristics of an organism.

The technique is still being perfected and, at present, there are a limited number of CRISPR clinical trials underway focusing on treating genetic conditions such as cancer, AIDS and blood disorders.

In theory, the technology could also be used to alter embryos with genetic conditions or prevent hereditary disorders from being passed on to children.

But ethical and scientific concerns mean editing embryos that will live to full term and 'germline' editing, which alters the genes passed on from parent to child, is illegal in many countries.

500,000

The number of human genomes the NHS hopes to sequence by 2023/24

- ▶ a part of the National Health Service (NHS), with the aim of producing half a million whole genomes by 2023/24. Other countries are doing the same and we can expect this trend to continue,” says Gallois.

“Using mass data, scientists will be able to correlate genomic sequences with disease conditions, identifying key DNA variants that may give rise to a disease condition, and enabling research focus on specific genomic conditions. This should result in improved diagnostic testing as well as targeted treatment therapies,” he adds.

While single-gene disorders have been the focus of research so far, these large-scale genome sequencing projects are also starting to unravel how genes interact with each other and the environment to cause disease. Using algorithms, researchers are assessing millions of common genetic variations associated with everything from heart disease to diabetes and obesity, and producing ‘polygenic risk scores’, which summarise the estimated effect of many genetic variants on a person’s predisposition to particular diseases. When fully developed, this technique could allow doctors to identify whole segments of the population at higher risk of particular diseases.

“By understanding a patient’s genome, medical authorities will be able to identify those people susceptible to particular genetic disorders, providing early detection and, if needs be, a focused therapy. The individual too can make informed behavioural decisions, maybe making lifestyle changes that may improve health outcomes,” says Gallois. BRCA1 was at the start of that journey, but its future potential is vast.

In addition to prediction, more accurate diagnosis and more targeted treatments, pharmacogenomics adds an

extra layer to the potential of genomics. “In the future, if you’re in a car accident, it may be that your genetic makeup will be on your ID card and so your treatment will take into account your specific genetic makeup needs,” explains Paroha.

However, as genomics is applied in ever more diverse ways, new risks must be addressed.

The risks to society

“My concern is that the more we know about our own genetic makeup there will be questions ethically of how much we will be obliged to disclose. Do you have to tell your employer what your genetic makeup is? Do you have to disclose these things to health and life insurers?” asks Paroha.

The complexity of genomics also opens up doors for the defence in health and safety lawsuits. “From a litigation perspective, your genetic makeup in the future could be argued as an alternative cause of your condition,” says Paroha, citing asbestosis as an example. “A company could argue that your genetics show that you’ve developed a condition not because of any external reasons, like where you work, but actually through your own genetic makeup.”

Gallois highlights data security as a key challenge. “Genetic data will increasingly be used to verify identity. The theft of that identity, as is the case now, could lead to financial loss.” Best practice at present includes de-identifying individuals’ data and ensuring that the data remains in a secure environment. “No such system is completely attack-proof despite the cyber protections afforded. We should also consider that, whilst at the moment technology does not provide for it, there could be



- ▶ a scenario in the future where that de-identified data could be made re-identifiable,” cautions Gallois.

Paroha explains that this risk is amplified when we take into account family groups. “We share around 50% of our genome with our close relatives so it won’t just be about our own personal data breach; it’s a whole family network privacy concern.”

There are also concerns over how much foreknowledge is too much. “We’re seeing some companies that will look at your cancer likelihood. But what does that information do for the consumer? Do you suddenly stop doing one thing that has an impact on something else, leading to a different problem?” asks Forrest.

However, one of the most eye-catching risks to society is the use of CRISPR technology, which allows for simple but powerful editing of genomes. Sometimes referred to as microscopic scissors, CRISPR potentially gives us the power to treat and even prevent many diseases by altering our DNA. “CRISPR has a powerful role to play going forward because rather than trying to optimise a drug, why don’t you just change the genetic defect, why don’t you just go to source and correct it?” explains Forrest.

From a safety standpoint, the fear is that by ‘germline’ editing - changing genes that are passed down the generations - in an attempt to cure genetic disorders, we will unintentionally create diseases that will become part of the gene pool. The major ethical concern is over where the line is between editing out debilitating genetic disorders and dialling up traits that society deems to be valuable, and who gets to decide.

“There are some CRISPR clinical trials for sickle cell anaemia treatments. That’s a single-gene defect, a

significant disease where you can have a very positive outcome, but that’s as far as it’s gone so far - single-gene defects. I see a small expansion in the type of genetic condition that gets treated and then there’s the decision about whether you want to have designer babies, because that’s where CRISPR leads,” says Forrest. “There are huge ethical questions around where the line is,” he adds. “At what point do you stop?”

This is one question society will need to face up to in the near future. “As we know with nuclear weapons, we cannot uninvent these things,” says Forrest, referring to the disparate regulatory environments around the world. “Ethically we are going to have to decide these things in the next five years because the tools are going to be there.”

Paroha says education is going to be critical. “Cultural and ethical standards are going to be examined and I think all of us need to know about genomics and how it’s going to affect our families. I think education is going to have to play a vital role.”

Life science market

One of the grey areas in terms of liability is around who is responsible for joining up the dots between a patient’s genetic profile and their reactions to drugs. “Is it drug companies’ responsibility to try and understand all the genetic and genomic aspects of the patient population they are targeting? Is it for academia? Is it for healthcare? Is it for governments?” asks Forrest. “That’s a tricky one because if you’re a drug company you can be closing down your market by figuring out more genetic information.”

However, Forrest cautions drug companies to think carefully about the impact of genomics. ▶

Key takeaways

- **Genomics is helping us to understand** how COVID-19 spreads, why some people are affected worse than others and how to fight back
- **Genomics allows us to understand** disease in a whole new level of detail
- **It is leading us towards more** predictive, personalised healthcare
- **Alongside the vast potential are** ethical and scientific risks
- **Drug companies' operating models** will need to adapt and evolve

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- ▶ “Manufacturers can’t take for granted that they shouldn’t be investigating particular genomic impacts of their products.” He is concerned about the potential for a wave of legal action around inadequate drug labelling and recommends strengthening instructions for use if there is research in the public domain linking genetic cohorts of people with adverse reactions.

The more human genomes that are sequenced and compared with medical records, the more patterns will emerge showing adverse drug reactions to existing products.

Forrest believes it is only a matter of time before regulatory pressure is brought to bear on drug companies and they are obliged to understand how genomics impacts adverse drug reactions. “You then need to figure out a companion test that goes with the prescription,” says Forrest. Such tests would check for genetic markers that indicate an adverse reaction might occur. “We’re going to see many more manufacturers not only wanting to do it but being forced to do it. Drug companies are going to have to develop companion tests and be active in the area of genomics as opposed to being passive.”

Future pandemics

It is hard to overstate the impact genomics is having on healthcare. And the speed at which our understanding of this field is advancing means that when we face pandemics in the future we will be far better equipped to tackle them quickly.

Forrest believes that, next time, genomics will be harnessed to make any restrictions on socialising hyper targeted. “I see a way in which we understand our immunity using genomic tools (immunomics), which will allow people to go on about their business and ultimately get others to shield,” he says. “Even out into the next six or 12 months we don’t know who’s had COVID, who needs the vaccine, who doesn’t. Whereas in the future you would hope we may have the tools to figure that bit out so that we could quickly get away from the economic carnage of having to lock everyone down and allow some functioning of society while also protecting those who don’t have the necessary antibodies.”

Indeed, we may look back from the next pandemic and say that we did not even have the language to describe what was happening during the COVID-19 pandemic.

The next report in this series will explore the impact of COVID-19 on supply chains.

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