INSTITUTE FOR MOLECULAR BIOSCIENCE

THE EDGE

Genetics

The latest in research and discovery

Knowing your ancestry
What are the benefits?

Genes vs environment
Is it nature or nurture?

Are you a super-taster?
The role your genes play

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Inside

Welcome

Inheritance has been an ongoing fascination for the human race. People have known for thousands of years that parents pass traits to their children, but it is only relatively recently that our technology has caught up to our curiosity, enabling us to delve into the mystery of how this inheritance occurs.

When the Institute for Molecular Bioscience (IMB) was founded in 2000, researchers around the world were engaged in a massive effort to produce the first sequence of the human genome. In fact, IMB was established to take advantage of this genomic revolution, and to connect genomics researchers with cell biologists and chemists to form a full pipeline of drug discovery.

The global effort to sequence the human genome took over a decade, and cost over $1 billion. Today, we can sequence a human genome in a few hours, for less than $1000. This advance in technology is powering a new era where treatments based on a person's genome are moving from science fiction to clinical reality.

All common diseases, such as heart disease and diabetes, have a genetic component; genetic factors contribute to 19 of the top 20 causes of death in Australia.

I'm proud that IMB is a world leader in harnessing genomics to improve the prevention, diagnosis and treatment of our biggest killers, with the ultimate goal being to develop personalised medicine based on an individual's genome rather than a one-size-fits-all basis.

Our researchers, such as Naomi Wray, Grant Montgomery, Peter Visscher and David Evans, may not be household names, but they are world leaders in their fields. Their work is changing how we manage diseases such as psychiatric disorders and endometriosis, and creating new methods used the world over to analyse the tsunami of big data being produced by genomics research. This extends to the next generation of researchers – Loic Yengo, Sonia Shah, Allan McRae and Quan Nguyen, who are developing exciting new ways to prevent the onset of disease, and treat conditions such as motor neurone disease and cancer.

Improving health equity is a high priority for us. IMB researchers are spearheading initiatives to increase the number of samples available for genetic research from non-European populations. Currently, more than 85 per cent of samples in genomic databases worldwide are from people with European ancestry, and this matters because factors such as risk of disease and response to medication can vary between populations. We are working to overcome these barriers and recruit people who reflect our diverse population.

This magazine is the third in our series *The Edge*, which explores some of the biggest health challenges facing our local and global communities. Please read on to learn how we are using genomics to overcome disease, and to learn more about how our genetics shape us.

Professor Ian Henderson
Executive Director
Institute for Molecular Bioscience
The University of Queensland

Genomics: decoding the blueprint of life

The study of genomics is ultimately the study of ourselves.

Our genome is a complete set of our genetic material, a copy of which is nestled in each cell in our body. Professor Naomi Wray shares how every aspect of us – from our height, to our eye colour, to our propensity for heart disease, even our choice of mate – is influenced to some degree by this microscopic material.

Our billion–year story

Our genome not only gives us insight into how we can have a better future, it also contains the story of our past. In every cell in our body is a copy of the history of our species, stretching back billions of years to the very first single–cell organism from which we are descended. By comparing genomes across different species, researchers can see where humans fit into the tree of life, uncover how we are related to other species and decipher the genetic changes that led to new branches on the tree, such as the evolution of mammals.

The blueprint of life

DNA serves as an instruction manual for how to build and operate a human and drives the changes that take us from a helpless baby to a fully–grown adult capable of scaling mountains, or developing complex algorithms to analyse our DNA. A key fundamental question we can address by studying genomics is why some people succumb to disease and others don't. By comparing the differences between people, we can pinpoint the genetic variations associated with traits, which provides a strong starting point for more research.

Even risk-taking behaviour has a genetic component

Predicting which medications an individual will respond to is a goal of genomics research

BY THE NUMBERS

Top causes of death in Australia to which genetic factors contribute

19 out of 20

All diseases involve genetics

Genetic factors contribute to 19 of the top 20 causes of death in Australia. The ostensible exception is death by accident, but even this can be debated, as your genes influence your personality, which can increase an individual's likelihood of risk-taking behaviour that may lead to an accident. All the others – including heart disease, dementia, cancers, diabetes – have a clear genetic component. Genetics also plays a role in infectious diseases, as was apparent during the COVID–19 pandemic, and the diseases and disorders that reduce the length of your life, such as psychiatric and neurological disorders. This means there is a lottery amongst children on who will be affected by a disease and who will not.

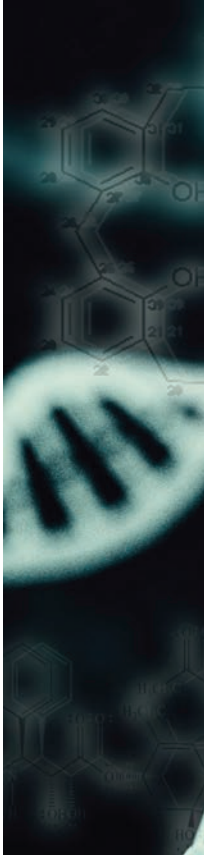
Clues to a better future

One of the ultimate goals of genomics is to contribute to the development of personalised or precision medicine, where prediction, prevention and treatment of disease are based on an individual's genome. DNA data allows a more accurate prediction of who is likely to get a disease, meaning people can be triaged into screening programs and raise the odds of preventing the onset of disease, which is better for both individuals and society as a whole.

Genetic research also allows us to answer questions such as why does a disease progress slowly in some people, and more quickly in others. Why do some people respond to treatment and others do not? Many promising drugs have failed in clinical trials because variable responses are reported between individuals. Can we use genetic information to work out which people are likely to respond to a particular medicine and make treatment decisions accordingly?

Who wouldn't be fascinated by these tiny molecules that have shaped us and our world?

DNA, RNA, genes and genomics – what's the difference?



Genetic information is passed on from parents to children via genes. But what exactly is a gene? And what is the difference between a gene and a genome? And how do DNA, RNA and chromosomes fit into the picture?

What is DNA?

Deoxyribonucleic acid (DNA) is the familiar double helix shape, the chemical code that holds our genetic information inside our cells. If unravelled, the DNA from one cell would stretch out to 2 metres long. The DNA in each of our cells is the same copy. The double helix 'backbone' is made up of alternating sugar and phosphate molecules with nucleotides, or bases, attached.

The chemical bases are adenine (A), guanine (G), cytosine (C) and thymine (T), which can be combined in any order to form the DNA sequence. There is a specific way that they pair for the structure to be stable: A with T, and C with G. As they pair and unpair, the double helix forms or unwinds.

What is a gene?

A gene is a segment of DNA that contains the instructions to build a protein.

Proteins do all the 'jobs' in our bodies – they include enzymes, hormones, antibodies, and structural proteins that support our cells and allow movement.

Gene expression occurs when genes are "read" by the cell and a protein is made.

Different genes are "turned on" in different cell types for the cells to perform their functions. For example, a liver cell has different functions to a heart cell, and therefore needs different proteins, which require different genes to be expressed.

What is a chromosome?

DNA is packaged into structures called chromosomes, ensuring that the DNA is tightly wrapped and fits in the nucleus of the cell. Each cell has 46 chromosomes, arranged in pairs – 23 inherited from each parent.

Cells are constantly dividing to create new cells to replace worn-out ones. When cells divide, all 46 chromosomes are replicated so a full set goes into each new cell, except when making egg or sperm cells, which only have 23 chromosomes. After fertilisation, when the egg and sperm fuse to make a new human, the full complement of 46 is met again.

What are DNA variants?

Most people have the same letter (A,G,C,T) at each of the 3 billion points of the DNA code, but at about one million points, it is common to find differences in the letters between people.

These DNA variants are responsible for some of the differences between people and are used in research. The key question is which DNA variants are important for risk of disease.

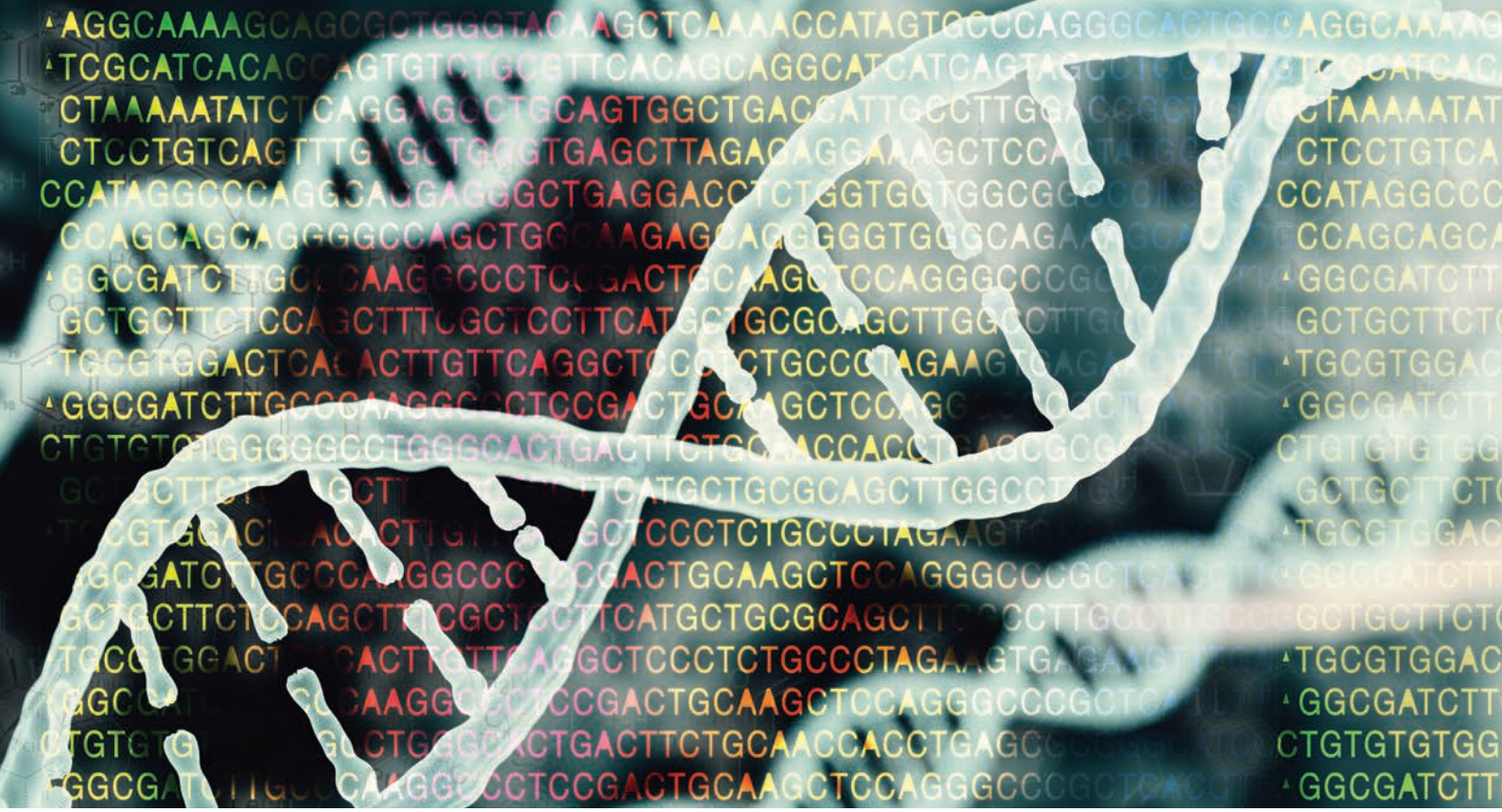
BY THE NUMBERS

Different species have different numbers of chromosomes

46 Human

14 Tasmanian devil

1260 Fern (adder-tongue family)

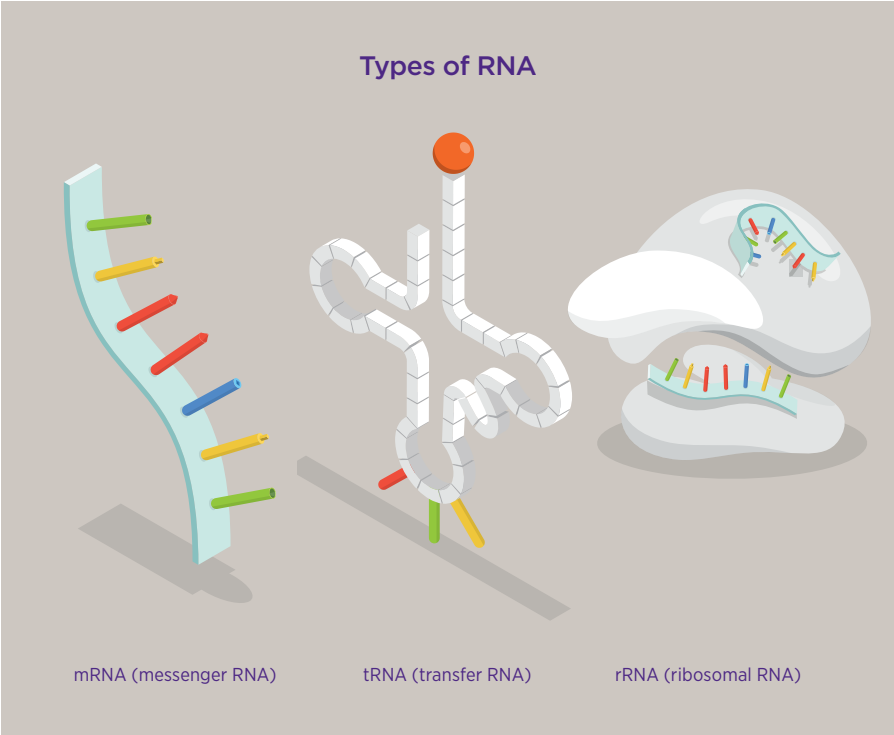


Chemical bases adenine (A), guanine (G), cytosine (C) and thymine (T) form the DNA sequence

What is RNA?

Ribonucleic acid (RNA) is single-stranded rather than double-stranded like DNA, and can pass out of the nucleus to the areas of the cell where proteins are assembled. It has A, G and C bases like DNA, but uracil (U) instead of thymine (T). Every group of 3 bases code for an amino acid, and proteins are made up of chains of amino acids.

There are three types of RNA in our bodies – transfer RNA (tRNA), messenger RNA (mRNA), and ribosomal RNA (rRNA) – that enact the DNA instructions to make proteins. You may have heard of mRNA in the context of vaccines, in which mRNA is used to trigger an immune response.



There are 3 types of RNA involved in making proteins

What is a genome?

Your genome is the sum of all the genetic information in your body, which encompasses much more than just our genes. In fact, only 2 per cent of our DNA meets the traditional definition of a gene, i.e. it contains instructions for making proteins.

The remaining DNA (around 98 per cent) used to be known as 'junk DNA', because scientists thought it had no function. But this theory has been challenged by many researchers including IMB co-founder Professor John Mattick. It is currently thought nearly 75 per cent of DNA produces non-coding RNAs, which have numerous functions such as turning genes on or off, or fine-tuning their activity.

Genetics vs genomics: what's the difference?

Genetics refers to the study of how genes work, what effect they have and how they are inherited by our offspring.

Genomics is the study and mapping of the genome as a whole, i.e. our complete set of genetic material, which includes genes, other DNA and RNA. It also encompasses the study of how our genetic material interacts with our environment to influence various traits.

Nature vs nurture

How are we influenced by our genes as opposed to our environment?

For some traits, genes play a very big role – for example, our height is determined 80 per cent by heritability, 20 per cent by our environment – and for other traits, the genetic influence is much smaller, like the number of children you have.

Researchers at IMB are helping resolve this long–running debate by quantifying the relative role of genes versus the environment for various traits.

Associate Professor Allan McRae (pictured left) explains why it is important to study the role of genes, even if there is only a small genetic component to a disease.

"If genes only play a small role, investigating their influence still gives us clues about the biology of the disease and starts to build up a complete picture – it also gives us ideas for potential drug targets.

"It's important to understand that genes and the environment are not entirely independent – the environment can be influencing your genes, determining if they are turned on and off."

Epigenetics – the environment influencing genes

So how does the environment affect our genes? This is where the field of epigenetics – changes to our DNA in response to our environment – comes in.

These epigenetic changes affect how cells use our DNA sequence, which in turns affects the production of proteins, which underlie nearly every biological process in our body. Epigenetic changes in response to the environment can potentially be reversible.

One change that occurs is when chemicals are added to our DNA. The most common chemical addition is methylation, when a molecule with a central carbon atom bonded to three hydrogen atoms – a methyl group – is added. Methylation is one of the ways in which cells control gene expression, i.e. turn genes on and off.

Another epigenetic change is when modifications occur to histones, which are the proteins around which DNA wraps. Every cell has a different pattern of methylation and histone modification, known as an epigenome.

"The epigenome gives a really interesting insight to a person's environment because it tends to get wiped at conception, so isn't inherited from your parents, and changes with age, environmental exposure and disease, meaning you can study how it has changed over time."

Dr Allan McRae

Embracing a healthy lifestyle and reducing stress can reverse some environmental changes to our DNA

Using the epigenome to predict age

"One thing we can do with the epigenome is to predict age, and there's a lot of research now into comparing people's real age with their 'methylation age'.

"People with a higher methylation age than their actual age have a higher risk of disease or may die younger, but maybe that can be reversed by leading a healthier lifestyle."

Predicting age using the epigenome could also have applications in forensics.

"Scientists could study the DNA of an unidentified body and use the epigenome to give an estimate of how old the person was when they died – we have an accuracy margin of about 5 years currently."

Epigenetics and smoking

Dr McRae and his colleagues have used epigenetics to look at methylation patterns in the DNA of smokers versus non-smokers.

"We found very big variations in methylation between smokers and non-smokers. Some of the variations that occurred due to smoking are reversible and some are still there 20 years after someone stopped smoking," Dr McRae said.

"Some methylation was heavily clustered around a hydrocarbon receptor – a gene that makes the protein that deals with detoxification of chemicals that you inhale when you are smoking.

"Sometimes the methylation pattern of a non-smoker looks like that of a smoker, then we discover that they live with a heavy smoker. Epigenetics doesn't lie – the person may not be lifting a cigarette to their lips but they are actually passive smoking and have the same amount of damage to their DNA as a smoker."

Epigenetics and disease

Dr McRae has a particular interest in epigenetics in neurodegenerative diseases such as motor neurone disease, Alzheimer's and Parkinson's diseases and also schizophrenia.

"The DNA is methylated at thousands of points across the genome so you compare the patterns in healthy people with the patterns in people with a disease or trait and find the differences.

"We don't know if the methylation is a cause or a consequence of the disease but the methylation still focuses around genes of interest – it gives us clues about how the disease works and potential targets for drugs."

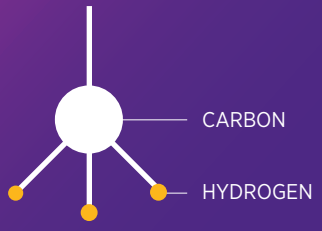
Environment is unpredictable and hard to control

Some environmental changes to our DNA are reversible – we can stop smoking, embrace a healthy lifestyle and reduce our stress in an effort to keep our DNA methylation down so we have a lower "methylation age".

Through evolution, epigenetics has allowed us to adapt quickly to our environment and for researchers and philosophers, it further blurs the distinction between what is influenced by our genes and what is influenced by our environment.

METHYLATION

A chemical reaction where a methyl group is added.



Knowing your ancestry

Have you ever been tempted to find out your ancestry by doing a DNA test?

Ancestry means different things to different people so we started by asking one of IMB's geneticists, Associate Professor Loic Yengo, what is ancestry?

"Unfortunately, there is no simple definition upon which all scientists agree," he says. "When populations are separated (for example, by continents) for many generations, genetic differences between those groups start to emerge. Some of these differences will be encapsulated by the concept of genetic ancestry."

"Frequencies of DNA variations differ between populations from different parts of the world, and some are explained by how long groups of people have been isolated from others."

But as populations mix, these genetic differences are reduced.

Blood types are an example of differences between continents – in Australia, 40 per cent of people are O positive, 31 per cent are A positive and only 8 per cent are B positive, whereas in India, the spread is much more even: 28 per cent of people are O positive, 25 per cent are A positive and B positive is the most common with 32 per cent of the population recording this blood type.

More recently, one genetic variant associated with COVID-19 susceptibility was found to be more frequent in people of European ancestry.

For the majority of DNA variants, changes in frequency over generations are purely random, in the same way that certain siblings can be taller than others while having the same parents. However, for a minority of genes, the specific environment (for example, the presence of an endemic parasite) may lead to a change in frequency, which geneticists refer to as "adaptation".

Sending your DNA to an ancestry company

When you send off your sample to an ancestry company, it is compared to DNA in reference data sets. These contain DNA from people who have good knowledge of their ancestry, for example, they know the birth places of all their four grandparents. If you have combinations of DNA variants that are only found in North Africans or Indians, then you most likely have ancestors from that region. Using these comparisons between your DNA and the reference data sets, you can find out what percentage you are of different ancestries, for example, 60 per cent North African, 10 per cent Finnish.

But as Dr Yengo explains, the reference populations become more informative as more data are added.

"As more people submit their DNA, your inferred ancestry could change slightly to reflect the fact that as more information becomes available, we are identifying more DNA variants overrepresented in single populations."

Home ancestry tests are cheap and easy, but do you want that information?

BY THE NUMBERS

The most common blood type in Australia is O+

The most common blood type in India is B+

Need for more diversity in data

"The caveat is, the more diverse the populations, the more diverse their environments – which creates more unknowns – this is what has pushed researchers to focus on relatively homogenous population groups in the past."

"A bias towards disease-associated DNA variants identified in people of European ancestry is a known problem in current genetic studies – and indeed this bias also exists in many other areas of medicine."

"Recognition of this issue is now driving initiatives to collect more diverse genetic data because it is critical to help identify disease-associated genetic variants specific to certain groups."

"It's a balancing act for researchers – getting rich data involves large sample sizes with diverse ancestry to help find more disease-associated genes and make the findings more robust, but it also means having to account for the environment and its influences in our calculations," Dr Yengo said.

Knowing your ancestry could help with personalised medicine

"Different ancestries can have different susceptibilities to disease. So, knowing your ancestry can help assess your risk of disease better, and inform appropriate steps with your lifestyle and have regular health checks."

"Also, as we move towards more personalised treatment, future medicines will be found to be more effective in certain genomes than others – for example, how quickly drugs are metabolised can vary between populations.

Knowing your ancestry can help drive decisions by doctors about which medicines to prescribe."

Disadvantages of testing

Are there any disadvantages to sending off your DNA for analysis? You could find out you are at risk of a certain disease or discover unsuspected relatives. However, most ancestry tests allow you to opt out of receiving information about your disease risk or family members. You can also contact a genetic counsellor if you have concerns about the results of a DNA test.

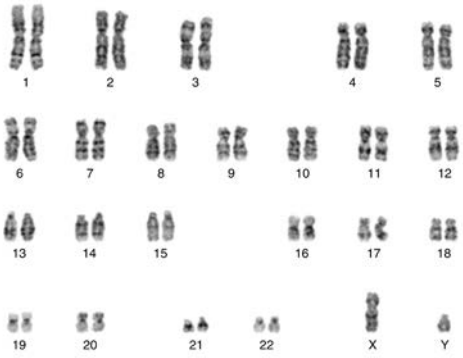
University research studies are closely regulated by research ethics committees, but the regulation of commercial companies is different, so it is important to read the small print carefully.

So, if you're on the fence about whether to explore your ancestry, go with a company that allows you to find out only what you want to know – you'll be learning about yourself while also helping research.

"Using more diverse populations increases our chances of detecting genes that correlate with diseases or traits."

Dr Loic Yengo

Types of genetic diseases



Genetic diseases or disorders are caused by a change in our DNA. These changes can be inherited from our parents, arise randomly or be triggered by an environmental exposure. A disease can be caused by a change in one gene (monogenic), changes to chromosomes (chromosomal) or by the small effects of many mutations or variations in combination with environmental factors (complex/multifactorial).

Monogenic

Monogenic disorders are diseases caused by a mutation in one specific gene such as sickle cell disease (hemoglobin-beta gene), cystic fibrosis (CTFR gene), Huntington disease (HD gene), or Duchenne muscular dystrophy (dystrophin gene). Genes code for proteins so a mutation in a gene can result in a truncated protein, a protein that can't fold properly or the protein prevented from being made entirely. When a protein is missing or can't perform its function, this can lead to disease.

Even though these diseases are caused by faulty versions of specific single genes, it is now recognised that their age of onset and severity depends on the actions of many genes and environmental factors.

Phenylketonuria (PKU)

All newborn babies in Australia are given a heel prick test soon after birth to screen for multiple rare diseases such as phenylketonuria. PKU is a rare disorder caused by mutations in the gene that codes for the enzyme that breaks down phenylalanine, an amino acid. Phenylalanine is found in all proteins in our diet, and if not removed by the enzyme, builds up to harmful levels in the body, causing permanent intellectual disability.

By testing at birth, babies diagnosed with PKU can be immediately placed on a diet low in phenylalanine to reduce their health risks.

Chromosomal

Chromosomal diseases occur when someone is born with changes to their usual 46 chromosomes. These changes can be numerical, meaning there is an additional or absent chromosome, or structural – part of an individual chromosome is missing, duplicated or moved to another chromosome. These changes occur when the egg and sperm are forming or during the very early stages of foetal development.

Down Syndrome

Down syndrome is caused by abnormal cell division early in development leading to a full or partial extra copy of chromosome 21. Down syndrome is also called trisomy 21, referring to the three copies of chromosome 21. This extra genetic material causes intellectual disabilities and developmental delay of varying severity.

Other chromosomal disorders include trisomy 13, trisomy 18 and changes in the sex chromosomes (XXX, XXY, XYY instead of the expected XX (female) and XY (male)).

The heel prick test screens babies for rare genetic diseases

Complex (multifactorial)

Most diseases – including the biggest killers such as cancer, coronary heart disease and type 2 diabetes – do not have a single cause. Instead, they are influenced by many genes in combination with environmental factors such as stress, exposure to chemicals and behaviours like diet and smoking.

The genetic contribution to these diseases has long been recognised through looking at family histories and how their risk runs in families. But as we investigate our genome in ever-greater detail, we are uncovering direct signals from DNA associated with common diseases. IMB researchers are developing statistical methods and software to analyse genetic and genomic data from millions of participants. These methods and software are used by researchers all over the world, extending their impact and amplifying the benefit of our research.

Building our knowledge about these complex diseases brings us closer to understanding them and devising ways to diagnose and treat some of the world's leading causes of death.

Heart disease

Heart disease is a classic example of a multifactorial/complex disease. There are many factors with a genetic component that contribute to heart disease, like faults in the heart muscle, rhythm or high cholesterol. Your inherited risk is set at birth, but whether you develop the disease will also be influenced by environmental factors, such as whether you smoke, exercise and eat a healthy diet.

A person who lives very healthily but has a high genetic risk may still experience heart disease, while someone who smokes, eats poorly and doesn't exercise might still manage to avoid it, thanks to good genes. Ultimately, we can't control our genes, so living healthily is the best way to minimise our risk.

Why don't all medicines work for everyone?

Part of the answer lies in our genes

There are many factors that influence our response to medication, including our size, foods we have recently eaten that affect absorption and other medications we are taking. Our genes can also have a big effect on whether a medication works for us, and how susceptible we are to side effects.

In many cases, differences in responses to medication can be due to faster or slower metabolism of a medication, so many studies involve searching for genetic variants that are linked to metabolism of a drug, a field of research called pharmacogenomics.

Ancestry plays a part

The number of genetic variants you have depends on your ancestry.

In 2021, the makers of the blood thinner Plavix were taken to court by the State of Hawaii and ordered to pay more than US$834 million to the state for failing to disclose that the drug could have a diminished or no effect in a large number of individuals of Pacific Island ancestry.

IMB's Dr Sonia Shah explains that the genetic variant that makes the drug ineffective is only present in around 2.5 per cent of the European-ancestry population but occurs in about 45 per cent of Pacific Islanders and around 60 per cent of South Asians.

"However, clinical trials of this drug were conducted mostly on people of European ancestry."

Diversity in research participants

"This is an important reminder of why diversity in research participants matters, especially when drugs are being developed for a global market," Dr Shah says.

The ability to combine pharmacology – the science of drugs – with genomics is another tool in the quest to develop effective, safe medications that can be prescribed based on a person's genetic makeup.

Response to medication can vary widely between patients

Which antidepressants work best?

Dr Shah is investigating how to better pinpoint which antidepressants will work for which patient.

"We don't fully understand how different antidepressants work, and we're also still learning about the biological changes in the body that may lead to depression. This means that currrently the only way to identify which treatment will work best is through trial and error."

"Some people may have to try three or four types of antidepressants before they find one that works for them, and this process may take many months."

Prediction instead of trial and error

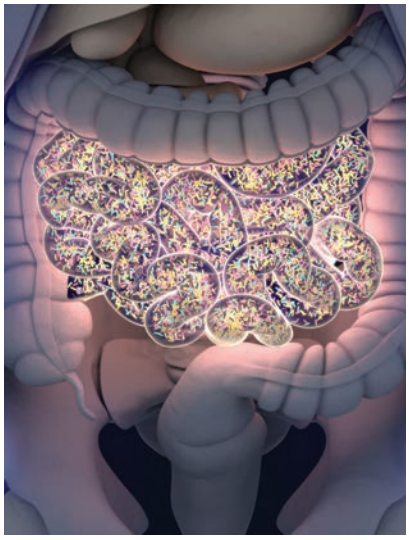
"We're hoping to speed up that process by growing up cells from these patients in the lab to try to predict the medication to which they are most likely to respond.

"Our hypothesis is that if we expose cells to an antidepressant in the lab, there will be differences in what genes get switched on or off depending on whether those cells come from someone who is known to respond to the antidepressant, or from someone who doesn't respond.

"These differences create a gene expression 'signature' for antidepressant response that differs between responders and non-responders, and could allow us to develop a simple blood test to predict the best individual treatment relatively quickly."

Busting myths about diet and disease

How genomics is being used to bust common myths



The gut biome describes the billions of bacteria that live in our gut, helping us digest our food

Autism and the microbiome

Picky eating has long been recognised as a symptom of autism spectrum disorder. Recent interest in the gut microbiome sparked the belief that this is because autism changes the make-up of the bacteria that live in the gut.

This belief has spawned a wealth of experimental treatments including faecal microbiota transplants and probiotics to attempt to change the gut microbiome and alleviate autism.

But do changes in our gut cause autism or does autism cause changes in our gut?

For her PhD research Dr Chloe Yap investigated the gut microbiome in children with autism and their siblings.

She analysed bacterial DNA from children's stool samples and found there was no direct association between autism diagnosis and the microbiome composition but there was a correlation between a less diverse microbiome and diet.

"We concluded that children with an autism diagnosis tended to be pickier eaters, due to sensory sensitivities or restricted and repetitive interests which leads to a less diverse diet, reduced diversity in the microbiome and looser stools," Dr Yap said.

"Our data suggest that behaviour and dietary preferences affect the microbiome, rather than the other way around."

What is a GWAS?

A genome-wide association study (GWAS) is a large-scale study to identify genetic variations in the DNA code, statistically associated with complex traits or diseases.

These associations are detected by comparing the genomes of individuals with and without the disease or trait to identify the genetic differences between these groups.

Commonly, 10 million (0.3 per cent) of the 3 billion letters in the DNA code vary between people, so these studies need to be large (tens of thousands of people) to get robust results.

A healthy high-fibre diet is recommended for those with DivD

Picky eating is often a challenge

Fibre vs genes

Diverticular disease of intestine (DivD) is a debilitating and sometimes fatal disease that, until now, was thought to be caused predominantly by a low-fibre diet.

PhD student Dr Yeda Wu was compelled to investigate the disease, fascinated that it is so common yet so overlooked.

Diverticula are sac-like protrusions in the wall of the intestinal tract affecting 33 per cent of individuals aged 50 to 59, increasing to 71 per cent in those aged over 80.

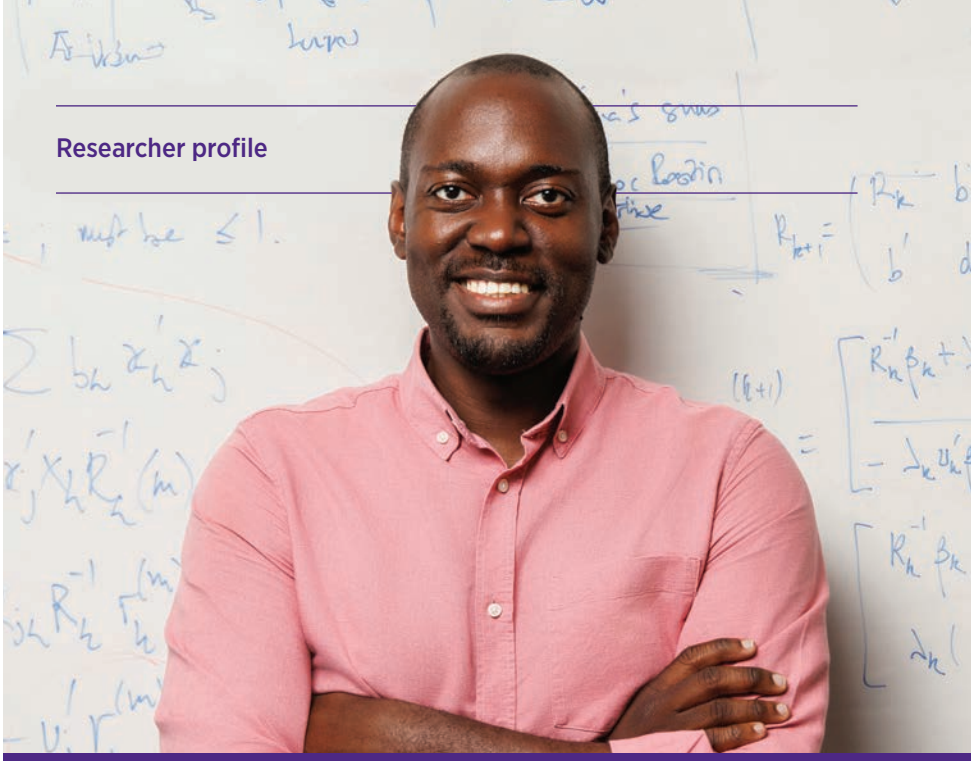
“A quarter of people with diverticula develop symptoms and even complications such as abscesses and bleeding, which can be life-threatening,” Dr Wu said.

“We were surprised to find that DivD is highly heritable, 40 per cent in fact, and our genome-wide association study of more than 700,000 people also identified 150 genetic factors linked to the risk of getting the disease.”

These genetic factors can be used to identify people who are at a higher risk of getting DivD so they can be monitored by their GP and encouraged to make changes to their diet to reduce the risk of developing the disease.

Studies like these also provide clues about how diseases are caused – some of the genes revealed were linked to colon structure, the layer of mucus in the gut and the processes that move food through the gut.

“While the genetics discovery is relevant for DivD treatment and prevention in the future, there is still a clear association between food intake and DivD,” Dr Wu said.



Researcher profile

Associate Professor Loic Yengo

Associate Professor Loic Yengo has always been fascinated by patterns. As a child, he loved the bright fabrics that his mother, a dressmaker, would use in their home in the Republic of the Congo.

But Dr Yengo’s affinity with patterns led him in a different direction – first, to a PhD in Mathematics in France, and then to running his own research group at IMB in Australia, where he investigates the patterns found in our genome.

A landmark study to predict disease risk

Dr Yengo is now embarking on an $8 million, eight-year effort to dramatically advance the prevention of chronic diseases, including diabetes, heart disease and cancer.

“Global health systems are currently threatened by the rise of chronic diseases that, to date, cannot be permanently cured,” he says. “Therefore, our best chance of reducing their burden is to prevent their onset.”

Dr Yengo is developing technologies that use mathematical models to accurately predict an individual’s risk of multiple diseases from their unique DNA profile. This will give doctors, patients and families a unique opportunity to prevent disease decades before symptoms occur, improving patient outcomes and reducing healthcare expenditure.

“The funding will also support the acceleration of this work into the clinic, so it’s available as a tool for doctors to use when doing health checks,” Dr Yengo says.

“For example, visiting the GP in 20 years’ time might involve a simple blood test from which they can advise your risk of developing various diseases, and prevention strategies you can use.”

Improving health equity for all

Dr Yengo says his group will analyse DNA sequences from millions of participants, with a unique focus on increasing participation of people with diverse ancestries.

“This study, funded by the Snow Medical Research Foundation, is an extraordinary opportunity to do this work at the necessary scale, including a 10-fold increase in the representation of people with non-European ancestries in genetic health data around the world,” Dr Yengo says.

This will help overcome the bias in risk prediction that has developed from previous genetic studies, which have mostly involved individuals of European ancestry, and ensure Dr Yengo’s discoveries benefit all communities worldwide, from Brazzaville to Brisbane.

Endometriosis

Using genetics to uncover the cause

Endometriosis is a complex syndrome that can affect 1 in 7 women of reproductive age, and result in constant and intense pelvic pain, fatigue, depression, anxiety and infertility.

It is caused by tissue that resembles the uterus lining, the endometrium, growing outside the uterus. Presence of this tissue outside the uterus can lead to the formation of lesions, cysts, scarring and inflammation.

Largest-ever endo study

Despite the severity of endometriosis, and the number of sufferers, we still have limited knowledge of the causes of this disease. Professor Grant Montgomery and Dr Sally Mortlock are using genetics and genomics to uncover more.

Professor Montgomery, Dr Mortlock and their team contributed to the largest-ever genetic study of endometriosis, finding new data about the variants that increase risk of the disease. The study involved 25 research groups from around the world, 60,000 women with endometriosis and 700,000 women without the disease.

Genetics gives us clues

"Endometriosis is a complex disease that can present in a variety of ways. Studying genetic risk factors can give us clues to the biological processes that are the basis for onset and progression of disease," Dr Mortlock said.

The new study has increased the number of genetic regions associated with endometriosis from 17 to 42, including new regions also associated with pain and other inflammatory conditions.

New treatments and quicker diagnosis

"We are following up these results to find out which genes in these regions increase risk and identify new drug targets, leading to new treatments."

The detailed genetic data also puts researchers and clinicians in a better position to diagnose endometriosis more rapidly – the symptoms are so varied and similar to other conditions that it has traditionally taken 8-10 years for a sufferer to receive a diagnosis.

With a family history of endometriosis herself, Dr Mortlock is driven to make a difference. "Rather than watch the next generation in my family suffer at the hands of this disease, I want to be the one that takes it on."

BY THE NUMBERS

1 in 7

women and those assigned female at birth have endometriosis

The invisible struggle: Laura's endometriosis story

Laura Terry thought she was used to pain. Her polycystic ovarian syndrome (PCOS) meant she had experienced cysts growing in her ovaries that would cause agony when they ruptured. But this pain was different.

"It was a radiating pain, it felt like all my insides and ribs were being crushed. It overwhelmed me and I couldn't walk and I ended up in hospital."

A new turmoil

"At the age of 30, I thought I knew everything about my body and my cycle, but suddenly everything was in turmoil."

After emergency surgery, Laura was told that the pain wasn't due to a cyst rupture. Instead, doctors had found endometriosis cells in her abdomen and she was diagnosed with endometriosis.

PCOS can have some similar symptoms, and in Laura's case, her PCOS initially masked her endometriosis. But despite the similarities, Laura can clearly distinguish PCOS from the pain she suffers with endometriosis.

"When a cyst ruptures, it can stop you in your tracks and make you fall over, but it leaves as fast as it arrives," she says.

Good days and bad days

"But the pain from endometriosis is much more and lasts for hours. It ends up with me laying on the floor, because I can't move, it's hard to breathe and I need to be as grounded as possible to deal with the pain.

"I have good days and bad days – on my good days I feel full of energy and happy and optimistic and I can talk about what I go through on the bad days."

Another concern for Laura is that she is in her childbearing years and now has been diagnosed with two conditions that can affect fertility.

"I do want a family and I've got close relatives – my grandmother, aunties and sister – who have had trouble conceiving, so it does cause me a great deal of stress."

Fortunate to have a diagnosis

But despite all these challenges, Laura considers herself one of the lucky ones because she has a diagnosis.

"Many people have to wait a decade for an endometriosis diagnosis, and I had mine very quickly. If I didn't have this diagnosis, I would question my mental health and other medical issues.

I feel that if more people were diagnosed, they would have answers to many of the questions they've been asking."

Laura is determined to raise awareness about endometriosis so that people's symptoms are validated, they can get the help they need and the disease is more relatable.

"I've learned quite recently that the number of women who have endometriosis is nearly the same as the number of people in Australia who have asthma – that was shocking to me."

Supporting research to reduce pain

"Most people understand what asthma is, but the awareness around endometriosis is still really low.

"I'm confident that research at IMB can reduce the time that people have to wait, fighting for a diagnosis, and cut the overall time that we are in pain.

"Everyone should support this research because it might not be you, but it could be your sister, your auntie, your cousin."

Endometriosis

The big leap between genes and function

Discovering the genes involved in a disease is vitally important for our understanding and designing treatments. But it's not the whole story.

IMB's Dr Brett McKinnon works on the genetics of endometriosis, and explains how to make the leap between knowing the genes involved in a disease and teasing out their function to ultimately impact treatment.

"Our lab contributed to a genome-wide association study for endometriosis and found 42 genetic regions associated with the disease. The next step for us is to look at how these genetic regions can influence gene expression, in other words, which genes are turned on or off in specific cells."

Every cell in our body has a copy of our genome, each containing the same genetic information. The reason heart cells are different from skin cells, for example, is down to the genes a cell turns on or off, which trigger instructions to produce different proteins and give the cell its unique function.

"Examining gene expression is a direct link between our genes and the function of the cells," Dr McKinnon says.

Mutations offer crucial clues

Mutations in gene regions associated with disease can offer crucial clues as to which genes are affected, and which functions are altered as a result of the mutation.

"Because of DNA's coiled structure, a mutation may affect a gene quite far away down the sequence, or the mutation could affect multiple genes."

Gene expression studies have been largely carried out on blood because it is relatively easy to access. But blood is a complex mixture of cell types, such as T cells, B cells, and macrophages. This mixture means cell expression data can only be taken as an average.

"When cells are all mixed together, it's really difficult to understand the function of a gene product at a tissue level – the genes that are expressed in a T cell are going to be completely different to those expressed in a macrophage, so you lose resolution."

The same challenge occurs when studying endometriosis.

Separating out the mixture

"We want to know what is going on in the endometrial tissue but that is also a mix of epithelial, stromal, immune and other cells," Dr McKinnon says.

To overcome this challenge, he grows each cell type individually in the lab, which allows Dr McKinnon to conduct cell-specific expression studies.

"We've been able to grow the different cell types separately in the lab, and we're also putting them back together to mimic what's going on in the body – we're creating three-dimensional replications of the endometrial tissue in a dish.

"We have the genetic data, so we can look at someone with a high genetic risk or a particular mutation, grow up their cells and see the effects directly.

"We are building up a repository of patients' cells that we can manipulate to harbour different genetic variants to start to understand how a person's genetics influence gene expression and the way disease develops."

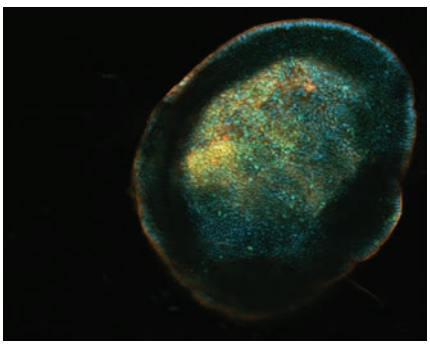
A personal approach

The next leap will be using cells from patients and the accompanying genetic data to screen drugs, or, in the future, growing up cells from lesions from a patient with endometriosis and testing which drugs specifically work for them.

Endometriosis is a very variable disease and having this personalised approach will make a huge difference to sufferers of a disease that currently has no targeted treatment.

"A patient can have different lesions in their body that respond to different drugs, so if we are able to target drugs to those lesions, which currently are being surgically removed, the impact will be significant."

Dr Brett McKinnon



An endometrial organoid grown from adult stem cells, prepared in IMB labs by Dr Sugarniya Subramaniam

Professor Naomi Wray and Professor Peter Visscher

"My own experience of how mental illness affects individuals and families motivates my research every day – and led to my interest in the genetic factors associated with disease risk."

Professor Naomi Wray still vividly remembers sitting in the library in North London aged 12, poring over a university-level textbook trying to work out her risk of mental illness in later life.

It wasn't a theoretical question.

"I learnt at an early age not to tell people that my father had a serious mental illness; my childhood drawings instead depicting him in hospital with a thermometer in his mouth," Naomi says.

Uncovering the risk of mental illness

"My own experience of how mental illness affects individuals and families motivates my research every day – and led to my interest in the genetic factors associated with disease risk."

Five decades later, Naomi is a world leader in understanding the genetic contribution to psychiatric and neurological disorders. And just as her personal life influenced her choice of career, Naomi's choice of career also had a significant impact on her personal life.

Professional and personal collide

While a PhD student in Edinburgh, she tutored a Dutch masters student. Peter Visscher would go on to become a professor, close collaborator of Naomi's – and her husband.

Peter is a world expert in developing advanced statistical models to handle extremely large data sets. This enables an understanding of the genetic basis of differences in risk of disease and other traits between individuals, such as height. Peter used height as a mathematical model for researching complex traits because it is easy to measure, has large data sets and is very heritable.

Peter and Naomi went on to establish a joint Program in Complex Trait Genomics, which together with their IMB genomics colleagues, is pushing the boundaries of genetics and genomics at the level of populations and individuals. They are particularly recognised for their pivotal role in developing Polygenic Risk Scores, which provide a quantitative measure of your genetic risk of a common disease.

Building connections for the future

Naomi and Peter are now sharing their significant expertise with the Big Data Institute at the University of Oxford – with a joint appointment with IMB, they are building strong connections to further boost genetics research and provide more certainty for children and families in the future.

Screening for risk or screening for perfection?

Some types of prenatal risk screening are routine in Australia but how far should we take this technology?

Until relatively recently, everything about a baby, including their sex, was a surprise when they were born. Advances in screening technologies mean we can now learn more about a baby while they are still in the womb – but should we?

Prenatal screening for chromosomal abnormalities is now routine in Australia and around the world – the mother gives a blood sample from which foetal DNA can be sequenced. Any abnormalities in the foetal DNA can be identified via this non-invasive prenatal test (NIPT).

Another screening test involves using a foetal DNA sample to generate a polygenic risk score, which is a number that predicts risk of developing certain diseases. This test is illegal to use on foetuses in Australia but available in other countries such as the USA, where some companies who provide IVF treatments offer this screening as part of their service.

Screening for common conditions

Some companies offer to screen embryos against more than 25 common medical conditions, for example, type 1 and type 2 diabetes; breast, prostate, and testicular cancer; malignant melanoma; coronary artery disease; hypercholesterolemia; hypertension; and schizophrenia. They also offer to screen for height, which is not a medical condition, and could be seen as a slippery slope towards selecting for traits such as intelligence.

Professor Peter Visscher, who helped develop the technology underlying polygenic risk scores, has advised caution about the use of these tests on foetuses.

"Where do we draw the line as a society? Will people be wanting to select the smartest embryo next?"

"We need more regulation in this space, and a society-wide conversation around using these technologies to select embryos because of the inherent uncertainty in some of these predictions.

Dealing in uncertainty

"For the genes with a big effect like BRCA 1 and 2 mutations, which increase the risk of developing breast cancer, this technology can be useful for people who have these genes running in their families.

"But for other common complex traits, such as heart disease, with many genes having small effects and much of the risk due to the environment rather than genes, there is so much uncertainty, and that's without even considering the ethics of selecting for traits such as height and intelligence."

Potential ethical and social problems

Professor Visscher says companies need to be careful what they are promising, and not mislead consumers about the accuracy of this information.

"Some genetic combinations will inevitably lead to disease, but many won't. To choose against an embryo because they carry genes that may or may not lead to disease is a much more serious proposition than advising an adult of their risk so they can make lifestyle changes.

"As for screening for other traits, it could potentially create huge ethical, social and maybe even psychological problems, if a child doesn't match their parents' expectations."

Testing for motor neurone disease using cell-free DNA

Motor neurone disease (MND) is rare but devastating, with patients slowly losing all their motor functions, such as walking, swallowing, and breathing, often dying within just 2.5 years following the onset of symptoms. MND diagnosis is currently plagued with elimination tests and sometimes unnecessary surgery. Researchers are hoping to change this by using cell-free DNA.

Dr Fleur Garton

Varying levels of cell-free DNA circulate in our blood

What is cell-free DNA?

Cell-free DNA circulates in our blood, as opposed to being wrapped up in the nucleus of a cell, Dr Fleur Garton from IMB explains.

"As our cells renew themselves, the contents from dead cells are broken down, recycled and short fragments of DNA end up in our blood," Dr Garton says.

"Our cells are always turning over so we all have cell-free DNA circulating, but your levels can change if you're pregnant, or if you have a tumour – so it can be a reflection of what's going on in your body at any time."

Cell-free DNA has already been harnessed for non-invasive prenatal tests (NIPTs) and liquid biopsies that test for cancer.

"I want others to be able to live life to the full and have every opportunity they deserve."

Dr Fleur Garton

Using cell-free DNA to research MND

The success of these tests and readily available technology spurred Dr Garton and collaborators from the University of California to investigate using cell-free DNA to progress research into MND.

"The fact that tests using cell-free DNA are already in the clinic removes a lot of barriers to translation – it's already been shown that it's accurate, efficient and economical," Dr Garton says.

"We hypothesised that MND patients have an increased cell turnover and high levels of cell-free DNA in the blood, and we found this was true.

"But it's not as straightforward as 'a high level of cell-free DNA is bad', as your levels can fluctuate with exercise or after fighting off a virus.

"We were really keen to try to understand what cells these fragments were coming from, so we measured the methylation of cell-free DNA."

A chemical clue

Methylation is one way in which gene activity is controlled and occurs when a chemical called a methyl group is added to DNA.

"Some methylation patterns are highly conserved across cell types, so we can look at methylation on DNA fragments and make an informed guess on which cell the DNA has come from."

Dr Garton and collaborators developed a method to estimate from where the DNA originated. While typically this is from blood cells, an increased proportion of the cell-free DNA in MND patients came from skeletal muscle, which is affected by the disease.

"We are now looking at the methylation status of cell-free DNA in a much larger number of blood samples and types of neurological conditions, generating data that will bring us closer to a sensitive test for MND.

"Our ultimate goal is a simple blood test to diagnose MND and track disease progression, which would be particularly useful whilst trialling new treatments."

A personal motivation

Dr Garton is driven by the need to develop better outcomes for MND by a deeply personal reason.

"My brother needs lifelong care due to a condition that is similar to MND," she says.

"I've made it my life's mission to carry out research that will make a difference to those who have these diagnoses."

Healthy hearts for all Australians

Most of us know the basics on how to keep our hearts healthy, but there are other risk factors for heart disease that are beyond our control, including our genetics.

Around 25 per cent of first-time heart attack patients have no traditional risk factors and lead active, healthy lifestyles.

IMB cardiovascular genetics expert Dr Sonia Shah said our genes hold important clues about why some individuals are more likely to get heart disease.

"Studying heart disease at a genetic level could not only help us develop new treatments, but also help prevent disease in the first place."

An unequal playing field

Heart disease is largely preventable.

"If we can predict who is at highest risk of developing heart disease, starting them on certain medications could help prevent a heart attack or stroke. Recent studies have shown that our genetic data can improve our ability to identify those at high risk."

But when it comes to predicting who is at high risk, the playing field is not equal.

The tools used by GPs to identify people who are at highest risk of heart disease are based on studies of mostly white people of European background, and are not as accurate in other populations. The same is true for genetic studies, where approximately 86 per cent of participants are of European ancestry.

"These risk prediction tools are underestimating risk in some groups, meaning individuals within these groups may not be getting timely access to potentially life-saving healthcare."

Increasing participant diversity is the first step

"Though past cardiovascular research has led to huge improvements in heart health around the world, historically, women and individuals of non-European ancestry have been under-studied. Therefore, the tools and medical guidelines used by the healthcare system may not be optimal for these groups.

"We want to address this inequity in heart health," Dr Shah said.

Her research aims to better understand risk factors for heart disease that are unique to women. Being of Indian ancestry herself, Dr Shah has also set up The South Asian Genes and Health in Australia Study to increase representation of Australians of South Asian ancestry in heart disease research.

Identifying those at high risk can help prevent heart disease

Keep your heart healthy

Eat a healthy diet with plenty of fruit and vegetables, wholegrains, healthy fats and low salt

Do regular physical activity – get active, setting small realistic goals to start and choosing activities that you enjoy

Quit smoking – smoking makes you four times more likely to die of a heart attack or stroke

Ask your doctor for a Heart Health Check

"Increased diversity in genetic and health research participants will ensure that the research we do today will benefit all Australians equally in the future."

Researcher profile

Dr Sonia Shah

Dr Sonia Shah has always been curious about the human body and how things work.

It's a trait she is putting to good use in her work: using genetic data to learn more about heart disease, with an ultimate goal of improving prevention, diagnosis and treatment.

Always having an interest in science at school, Dr Shah found biology was her favourite subject, which eventually led her into bioinformatics – the application of computing tools to analyse biological data.

Research close to her heart

"Whilst working as a bioinformatician, I was asked to work on a cardiovascular disease genetics project, and I really fell in love with it.

"This research is very close to my heart – after being diagnosed with type 2 diabetes, my dad did everything right. He changed his diet, exercised regularly and lost a lot of weight. So, it was a huge surprise when, a few years later, a heart health check revealed three blocked arteries and need for a triple bypass."

Dr Shah has established her own research group and works closely with doctors to ensure her research is answering clinical questions.

"I want to make sure we are addressing the gaps in our knowledge, driven by clinical needs. Risk factors, symptoms, disease severity, and even response to medication can vary by sex and ethnicity, but we lack data in women and those of non-European ancestry. I'm hoping our work will contribute towards reducing existing inequity in cardiovascular healthcare."

A positive impact through mentoring

Dr Shah is also hoping to make a difference in the lives of young women and girls who are interested in pursuing a STEM career.

"The most challenging part of my career has not been deciphering the complex information contained in our genome, but rather returning to work after having a baby," she said.

"If it wasn't for the support of my mentor, Professor Naomi Wray, I may have given up at some point and just said, 'This is too difficult'.

Dr Shah is now paying this help forward by mentoring female high school students who are passionate about science.

"My career path has not been linear, and an academic career was never intentional. I've realised that sharing my experience with building a career while raising a family can have a positive impact, and mentoring is something that I have found highly rewarding."

It's a lesson her two daughters are also learning, as they see Dr Shah making mentoring calls from the car as they head into gymnastics lessons.

"I hope I am laying the groundwork to not only kindle a passion for STEM in my daughters, but also to help ensure they have fewer barriers to hurdle over than I did."

Genetics of handedness

Are you a leftie or a rightie?

'Handedness' is the preferential use of one hand over the other. You don't need to be a scientist to know that preferring your left hand is much less common, but did you know that rates of left-handedness vary round the world from 3 to 12 per cent?

Rates tend to be higher in more permissive societies, and lower in more formal societies and those where people traditionally eat with the right hand and clean themselves with the left hand. Rates of left-handedness have also changed over time, as the stigma of using the left hand abates.

The least inherited of any trait

Hand preference is first observed in the womb as embryos begin to show single arm movements so it's surprising that it is actually one of the least inherited of any trait. The ratio of the influence of genetic factors to environmental factors varies from trait to trait – in handedness, genetics only has a 25 per cent influence on variation.

Professor David Evans is IMB's expert on handedness and explained why researchers are so interested in a seemingly superficial trait.

Learning about the brain

"There's a lot we can learn from studying handedness because it is correlated with what's going on in the brain – for example, if you are right-handed, you are more likely to have lateralised brain function – that's function on one side of the brain, such as language centres.

"If you're left-handed, you are more likely to have less lateralisation so may have language centres in both hemispheres of the brain. This doesn't mean left-handed people are more skilled with language.

"If we've got a good understanding of laterality in the brain then that helps equip us to develop treatments for stroke, epilepsy, or trauma where you've got damage to a particular part of the brain."

BY THE NUMBERS

Number of left-handed Australians

10%

"Nobody knows what causes handedness, so if we can find genes that are somehow involved in determining if someone is left– or right–handed, that gives us clues to the underlying biology."

Genes influencing handedness

Researchers also study handedness to better understand the causes and consequences of left-handedness on risk of disease and other traits.

In a 2020 study, Professor Evans and his team identified 48 genetic variants with strong links to handedness.

"We found that 41 of these genetic variants influenced left-handedness and seven were associated with ambidexterity, which occurs when a person is equally proficient with each hand.

"Nobody knows what causes handedness, so if we can find genes that are somehow involved in determining if someone is left– or right–handed, that gives us clues to the underlying biology."

Some of the genes they found play a role in the development of brain cells and the flexibility of the brain to adapt to change, which could explain the ability for people to teach themselves to write and perform other activities with their non–preferred hand.

Maybe it's time to try that left–handed bowling, because in the case of handedness, genetics is only part of the story.

Rates of left handedness are higher in more permissive societies

Eye colour is complex genetic trait, controlled by over 60 genes

The complexity of eye colour

Eye colour is still used to teach genetics in school, with students learning brown eyes are dominant over recessive blue eyes.

BY THE NUMBERS

79%

of people in the world have brown eyes, making it the most common eye colour

This is a hangover from the days when it was believed that eye colour was determined by a single gene, with one copy inherited from each parent and the eye colour of the child determined by the most dominant version.

It caused some confusion when blue-eyed parents had a brown-eyed child!

A continuum of colour

Now we know that eye colour is a complex genetic trait, controlled by multiple genes that produce a continuum of eye colours that move through a spectrum of brown, amber, hazel, green, blue and grey. But the myth of a single gene for eye colour is still perpetuated, probably because it is a simplistic teaching tool.

One of the main genes that influences our eye colour is OCA2. Eye colour is related to the amount of melanin – molecules that produce pigment, among other functions – in the front layers of your iris. Brown eyes have a large amount of melanin and light blue eyes have much less.

OCA2 is involved in the production, transport and storage of melanin. Oculocutaneous albinism, which results in very light skin and light-coloured irises, is caused by a mutation in *OCA2*. A specific mutation in a sequence within the adjacent HERC2 gene regulates the function of OCA2 and plays a role in blue/brown eye colour. Other genes with lesser effects are also involved in skin and hair colouring.

Over 60 genes taking part

In 2021, IMB's Professor David Evans collaborated in the largest genetic study of eye colour to date, to find out if there were more than 11 genes involved in eye colour.

"We were surprised to find a further 50 genomic regions associated with eye colour – many of these genes were linked with melanin pigmentation, but we also found others associated with the structure and formation of the iris," Professor Evans said.

"This study clearly demonstrates that the genetic complexity of human eye colour considerably exceeds previous knowledge and expectations."

So if you learnt the 'one gene, one colour' basic genetics, it's back to school!

Are you a super-taster?

Have you ever wondered why Brussels sprouts are the least favourite vegetable at Christmas? Or why a freshly brewed coffee might taste great to you but have your friend pulling a face?

IMB's Dr Daniel Hwang says taste is influenced by the interplay between genetic and environmental factors. "While it is inherited from our parents, it can still be dramatically changed by environmental influences – your culture, your exposure to a food, an illness causing loss of smell – many things can change your perception."

Comparing twin tastes

Dr Hwang's interest in the genetics of taste all started when he worked in the USA and got involved in testing the tastes of identical and non-identical twins.

"The Twins Days Festival is the largest gathering of twins in the world and is held for a few days each year in Twinsburg, Ohio – there's opportunities for the twins to get involved in research studies. We travelled there with a big box of different taste and smell tests and compared responses from hundreds of twins."

Sweet, sour, bitter, salty, umami, astringent, pungent

The most heritable taste, coming in at 70 per cent heritable, is the perception of phenylthiocarbamide (PTC) – a very bitter taste similar to the bitterness found in Brussels sprouts.

"We call people who find PTC extremely bitter 'super-tasters' and they make up 20 to 25 per cent of the population," Dr Hwang explains.

Everyone has two copies of the bitter taste receptor gene TAS2R38 – one from each parent, and the copies can vary. 'Super-tasters' have two functional copies, 'tasters' have one and people with no functional copies are 'non-tasters'.

"Being a super-taster determines your preference for Brussels sprouts and cucumbers – you are also less likely to put salt on your food."

Twin studies are used to identify if a trait has a genetic component by comparing identical twins, who share all their genes, and fraternal twins, who share 50 per cent. If a trait is found to be more similar in identical twins, it is more likely due to genetics.

Dr Daniel Hwang

But in studies of older people, the super-tasters were less likely than their younger counterparts to fuss over the vegies in their roast dinner.

"As we get older, we lose taste buds so Brussels sprouts taste less bitter. We could also get used to the taste, or get to like bitter tastes more or cook our Brussels sprouts differently."

Youth are more fussy?

To explore this phenomenon more, Dr Hwang studied the tastes of younger Australians, serving up tests to over 2000 people aged 13 to 25 years.

"Young people are less influenced by the environment, so we find that most of the super-tasters respond to the tests as we'd expect – they really don't like Brussels sprouts.

But why do our genes direct our taste preferences so much?

"Humans naturally like sweet because foods that taste sweet are often high in energy – it's an evolutionary consequence that we look for sweetness to survive. Meanwhile, we don't like bitter, because most of the bitter stuff in nature is toxic and our bitter taste has evolved as a defence system to prevent us from swallowing poisonous foods."

"Being a super-taster determines your preference for Brussels sprouts and cucumbers – you are also less likely to put salt on your food."

The danger of bitter

The potential danger of bitter seems to outweigh the lure of sweet, which is only 30 per cent heritable. Nintendo has harnessed this distaste, using a bitter-tasting agent called denatonium benzoate on Nintendo Switch game cards to stop kids putting them in their mouths.

Other bitter substances include quinine, the source of bitterness in tonic water, and caffeine – your bitter taste perception can determine how much coffee you drink.

When you lose taste

One of the ways Dr Hwang is using his rich treasure trove of taste data to help people is studying how the loss of taste caused by radiotherapy affects cancer patients.

"We're studying the effects of radiotherapy on taste and appetite – does your sense of taste return more quickly if you are a non-taster, taster or a super-taster?

"It's hard to eat when you can't taste, as you can't be bothered, and we want patients to be eating as healthily and as well as possible during their treatment."

Brussels sprouts have always been controversial on the dinner table but now we know genes play a part

Do genes control our behaviour?

The data says yes and many of our behaviours can be predicted, including our choice of partner

Traits like eye colour and disease risk run in families and are influenced by our genetic makeup. But did you know that your genes also influence your behaviour?

But how do we know this? If you have grown up in the same environment as your parents and siblings, how do you know if that mannerism from Dad is inherited or learned?

Associate Professor Loic Yengo is analysing our genomes to find DNA variants that are associated with human behavioural traits.

"It turns out we can predict many behaviours such as the years of schooling that person is likely to have, their likeliness to migrate for opportunities, their propensity to smoke or take risks and their choice of mate," he says.

Choosing a partner

"One of the classical assumptions in genetic studies is that people look for partners randomly in the population, but our analysis of genetic data shows that this isn't true."

Dr Yengo's research has confirmed that most people choose partners who are similar to themselves.

"We know that the height of partners are correlated, though not extremely highly, for example, tall people tend to choose tall partners. "And even if partners may not look like each other, they often have other similarities that may not be immediately obvious."

Shaping the next generation

"I'm interested in these questions because our choice of mate shapes the next generation, including the likelihood of children having risk factors for disease. We can predict by how much social inequalities will increase if people tend to select partners with a similar level of education."

But is this just a case of people choosing similar partners because that is whom we're exposed to?

Interestingly, the answer is no.

A study in South Korea after the introduction of online dating found that the more choice people had, the more they chose partners who were similar to themselves. The same holds true in studies conducted by Dr Yengo and collaborators in European and Japanese people.

"While you may want to think your behaviour and choices are entirely your free will, your genes have more of a say than you think."

The future of genomics

Genomics is a rapidly evolving field. Discoveries made by researchers now have the potential to change healthcare in the future. We asked five leading IMB genomics researchers what advances they are most excited about in the next 5 to 10 years, and the implications for healthcare.

Professor Naomi Wray

Personalised medicine for depression

We are on the cusp of a new era where personalised medicine will be reality, even in psychiatry, which I'm excited about.

We are starting to link genetic variation in people to variation in their cell-based phenotypes – their traits and their clinical data.

Cell models that enable us to make this link are becoming cheaper and more scalable, allowing us to accelerate our investigations into which genetic variants influence traits.

These models include induced pluripotent stem cells – skin or blood cells that are reprogrammed back into stem cells that can be stimulated to develop into other cell types of the body – and organoids – cells growing in the lab in 3D structures.

To take advantage of our growing understanding of how genetic variation plays a role in disease, we are launching the Australian Genetics of Depression Cell-omics Study to create a new resource internationally for depression.

Our ultimate goal is that when someone presents with clinical symptoms, they will have a blood test leading to a diagnosis with an accompanying treatment, for example, "a psychiatric disorder responding to SSRIs (selective serotonin reuptake inhibitors)" could be inferred from cell-based phenotypes. These approaches will also lead to ideas for prevention – a word that is under-used in psychiatry research.

Professor David Evans

Using 'mega-studies' to identify new treatments

Due to recent advances in genotyping technology, the cost of sequencing an individual's genome has plunged from literally over a billion dollars in the early 1990s, to well under a thousand dollars today. It is now financially possible to sequence the DNA of millions of individuals contained within large-scale biobanks across the world. Many of these biobanks also contain information on patients' health through linked clinical records and extensive deep phenotyping information, which record an individual's physical traits. There are currently efforts underway to combine this information across multiple biobanks in genetic mega-studies. Genomics researchers could mine these data to identify genes that cause disease, create algorithms to determine an individual's risk of disease in the future, and use this information to identify targets for future drug therapies.

Professor Grant Montgomery

Targeted treatments for endometriosis

Spectacular advances in genomics and computing have greatly increased our understanding of disease in individuals and different groups from population-scale datasets down to single cell differences in space and time.

While challenges remain with the integration and management of very large datasets of detailed individual data, there are exciting practical applications that challenge healthcare to provide more personalised medicine. Examples include better individual treatments, greater recognition of disease subtypes and better targeting of drugs and drug doses to reduce variability in treatment responses.

In our endometriosis research, we are combining clinical data with genetic risk factors to shorten the long delay in diagnosis and reduce the need for unnecessary surgery. We also employ high-throughput genetics and genomics screens in organoids of individual patients to identify molecular markers for subtypes of endometriosis, discover new drug targets, and help predict and prevent recurrence after treatments.

Dr Quan Nguyen

Treating cancer one cell at a time

Cancer originates from one aberrant cell that can expand locally in the surrounding tissue, and might eventually spread to other organs and reach an incurable metastatic state. For more than 150 years, cancer has been observed under a microscope by trained pathologists, recognising the aberrant appearance of cells to provide essential information for diagnosis and treatment. However, they cannot see the molecular profiles of the genes and proteins underlying the disease, which provide another layer of information.

My lab combines the techniques of single cell sequencing and spatial technology to study cancer in more detail than ever before. Single cell sequencing allows us to understand genetic codes at the resolution of a single cell, the building block of the human body. Spatial technologies measure molecular profiles within a tissue whilst preserving the location of cells and their neighbours, adding thousands of layers of molecular information to traditional methods.

Using these techniques, my lab can study cancer one cell at a time and across all cells within tissue across multiple time points. We aim to find new gene and cell biomarkers for early and accurate diagnosis. Controlling the spread of cancer cells is often not precise because drugs affect multiple cell types, including healthy cells. Our research will find new targets that drugs can interfere with precisely and effectively so cancer can be cured with a higher chance of success and a lower risk of side effects.

Overall, we hope our genomics work on single-cell and spatial analyses of cancer patient cells and tissues will contribute to curing cancer in the future.

Dr Sonia Shah

Moving away from ‘one size fits all’ to precision medicine

Our genetic makeup determines how likely we are to develop disease, how severe our symptoms may be – for example, some people with COVID-19 had very few symptoms, while others got long-COVID or developed heart failure. Our genetics also affects how we respond to medication and whether we are likely to have an adverse reaction.

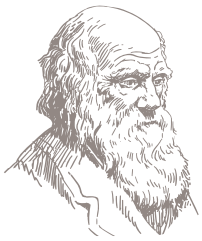
Moving away from a ‘one-size-fits-all’ approach to healthcare, we are now rapidly advancing towards the exciting era of ‘precision medicine’, where our genetic data could be used by doctors to provide healthcare that is tailored to our genetic makeup. Countries like the United Kingdom, Finland and Singapore are already ahead in this race.

Integrating our genetic information in healthcare has the potential to reduce the burden of disease, improve disease diagnosis, improve treatments, reduce serious adverse reactions to medication and ultimately lead to major improvements to healthcare. But we need to ensure these benefits are felt equitably by all populations.

As we move towards precision medicine, we urgently need to address the lack of diversity of participants in genetic studies, 85 per cent of whom are currently of European ancestry. Findings from one population do not always translate well into other populations. We have launched the South Asian Genes and Health Study to encourage more samples from Australians of South Asian descent, and provide a framework for more inclusive genomics research in Australia.

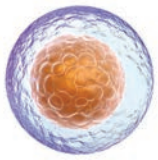
DNA

A timeline of discoveries



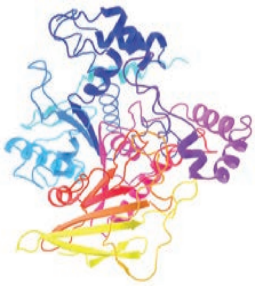
1859

Charles Darwin publishes *On the Origin of Species* – describing his theory of evolution by natural selection



1869

Friedrich Miescher isolates DNA from cells for the first time and names it "nuclein"



1944

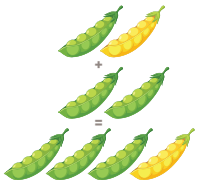
Tatum and Beadle show that genes code for proteins

1953

James Watson and Francis Crick describe the double helix structure of DNA

1977

DNA is sequenced for the first time by British and American scientists working independently, using DNA from bacteria and viruses

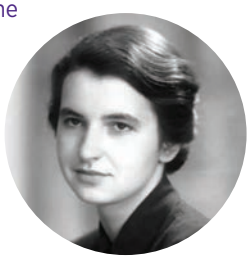


1865

Gregor Mendel, the "Father of Genetics", uses pea plants to demonstrate the laws of inheritance

1952

Rosalind Franklin and Raymond Gosling photograph crystallised DNA fibres, visualising the structure of DNA for the first time



1964

The genetic code is cracked: researchers show that RNA, copied from DNA, is the template for making proteins

400 BC

Ancient philosophers hypothesise about the mysteries of inheritance – how do features of parents get combined and transmitted to offspring and what gets passed down?

10000 BC

Humans begin to selectively breed livestock and crops, showing some understanding of inheritance

1911

Thomas Hunt Morgan and his students study fruit flies and show that chromosomes carry genes, and demonstrate genetic linkage, which can be used to calculate the order of genes on a chromosome

Inheritance has always been a fascination for humankind, but once DNA was discovered, research progressed at a rapid pace. Sequencing technology and computing tools have lifted advances to a whole new level and in the last 20 years, the rate of discovery has been exponential.

1988

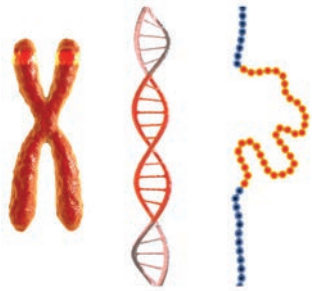
IMB's Peter Koopman co-discovers the gene on the Y-chromosome (SRY) that leads to development of male characteristics in mammals

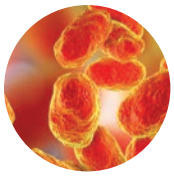
1990

The Human Genome Project is launched – an ambitious project to sequence the entire human genome

1983

The first disease-associated gene – a genetic marker for Huntington's disease – is mapped to a human chromosome





1995

The complete genome of an organism is sequenced for the first time – the bacterium *Haemophilus influenzae*

1997

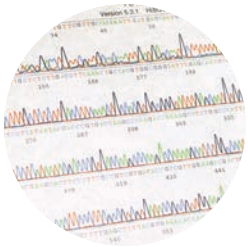
The Universal Declaration on the Human Genome and Human Rights is issued by the United Nations

1996

The first mammal is cloned from an adult cell – Dolly the sheep

2003

The first draft of the Human Genome Project is completed, taking more than a decade and costing over a billion dollars



2006

Rapid, high-throughput, low-cost sequencing technology is developed, enabling whole genomes to be sequenced in a single run

2006

UK Biobank starts recruiting 500,000 participants, providing a unique database of health data, crucial to large-scale genomic studies

2007

The first large genome-wide association study (GWAS) for common diseases is completed by the Wellcome Trust Case-Control Consortium, including IMB's David Evans

2010

IMB's Peter Visscher leads a project that shows "missing heritability" for complex traits is caused by thousands of DNA variants, each with a tiny effect

2022

IMB researchers lead the largest-ever GWAS of nearly 5.4 million people to uncover 12,000 genetic variants linked to height

2012

CRISPR-Cas9 technology is introduced, allowing rapid, low-cost gene editing and potential for gene therapies


Imagine predicting disease decades before symptoms occur
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where the next cure begins
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