Annual Review

Ideas | Ingenuity | Impact

wellcome trust

Illustration by Travis Bedel, commissioned for the Wellcome Trust

Contents

People with great ideas can transform lives

JEREMY FARRAR

Two achievements made with Wellcome Trust support this year demonstrate the breadth and depth of what we do to help improve health in the world.

In February 2015, the UK Parliament made it possible to license new techniques to prevent mitochondrial disease. These are devastating conditions (see page 6), but the idea for how to prevent them came directly from years of scientific research to understand the basic biology of mitochondria and what happens when they don't work properly.

> "THE WELLCOME TRUST CAN COMBINE A LONG-TERM PERSPECTIVE WITH SWIFT ACTION"

More research followed to ensure the new techniques would be safe, as well as public consultations and ethical debates because they involved replacing faulty mitochondria with healthy donated mitochondria at the earliest stages of pregnancy. Convinced they were essential life-saving procedures, we joined patient groups and our researchers in campaigning for the legislative change that would allow them to be licensed in the UK. We now look forward to these techniques being used to allow families at risk of mitochondrial disease to have healthy children.

The other achievement is a vaccine for Ebola that we helped to get into clinical trials during the epidemic in West Africa (see page 11). In August 2015, interim results were published, and they were spectacular. The trial design meant that when someone was diagnosed with Ebola, their family, friends, neighbours and other contacts were all offered the vaccine. More than 2,000 people in Guinea received the vaccine immediately after being identified as a contact, and none of them got infected with the virus.

While this success is remarkable, the world should have been so much better prepared. The vaccine was developed five years ago but hadn't been tested in people. It took an astonishing collaborative effort to set up and run the trials so quickly – but it was not quick enough for thousands of people who died of Ebola in the first year and a half of the outbreak.

At the time of writing, the epidemic is not over – this vaccine could help bring it to an end. But while efforts continue in Guinea, Sierra Leone and Liberia to stop Ebola and to recover from its serious knock-on effects, we need to think now about what we as a global community might be facing next time – whether it's Ebola or another disease for which we are currently underprepared. There are so many infections around the world that have the potential to cause serious

Liberian six-year-old Cecelia, holding a sign made by Alphanso Appleton, the son of an Ebola survivor. *Photography by Alphanso Appleton*

outbreaks in people, a problem made worse by the rise of drug-resistant infections. We need to coordinate research to understand new challenges, to develop diagnostics, treatments and vaccines, and to be able to start assessment as soon as possible during an epidemic. Ethical and regulatory protocols should be agreed in advance, as well as contracts for production and delivery. We must also appreciate and understand the social and cultural context in the communities where these epidemics emerge.

Preparedness is often talked about in global health, but it has been allowed to drift. We and our partners are pushing for change, for reformed international bodies that are capable of ensuring the world is as ready as possible for emerging infectious disease threats.

A new approach

Being an independent charitable foundation, the Wellcome Trust can combine a long-term perspective, funding research that might take years to result in health benefits, with swift action to meet urgent needs or harness new opportunities to transform lives.

That's the core of our philosophy, and it underpins the new strategic approach we published in October 2015. This frees us to act more decisively in priority areas, as well as continuing to support people who come to us with great ideas in any field of research related to health.

You can read more about our strategic approach on page 4 and on our dedicated website (strategy.wellcome.ac.uk). Our initial priorities include vaccines for neglected diseases, drug-resistant infections, improving diversity, and encouraging more research to understand links between the environment and our long-term health.

Another is building partnerships in Africa and Asia so that more scientists can pursue research into the most pressing challenges in their regions. This work is already underway (see page 14) and I'm proud that we are shifting the centre of gravity for leading research towards places where the burden of disease is greatest.

I hope you enjoy reading about more of our work in the *Annual Review*. As ever, we extend enormous thanks to all those who helped us this year by reviewing applications and sitting on our advisory committees – a vital contribution and a reminder that we are at our best when we bring people and ideas together to improve health for everyone. A very personal thank you to Sir William Castell, who stepped down as Chair of the Wellcome Trust this year. Bill oversaw a decade of innovation and achievement, and I very much look forward to working with his successor, Eliza Manningham-Buller, in the years ahead.

Jeremy Farrar,
Director, Wellcome Trust

Past, present and future

CLARE MATTERSON

History has always been important at the Wellcome Trust. Sir Henry Wellcome, our founder, had two big archaeological excavations in progress when he died in 1936, part of his lifelong fascination with the roots of human culture and the history of medicine in particular. His legacy was to support scientific and medical research to improve health, but he made sure that we would also support research to understand the social and cultural contexts of health and medicine.

> “NOT EVERY EFFORT WILL SUCCEED, BUT THOSE THAT DO WILL TRANSFORM LIVES”

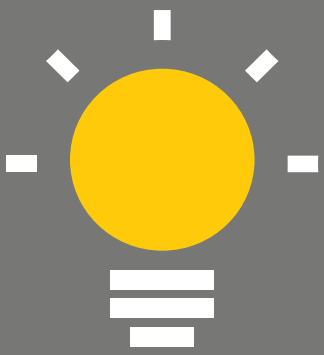
It's a successful legacy. Over the past 80 years, through scientific research we have contributed to the development of frontline drugs for malaria, the sequencing of the first human genome, innovative diagnostic devices, psychiatric therapies, and techniques for preventing disease. We have led transformations in the medical humanities, open access publishing, science education, research careers, and engaging people with science.

Each of these achievements involved a lot of people and a lot of ideas coming together over a number of years. Our history, then, is one of helping great ideas improve health, and this remains at the heart of our new strategic approach, published online in October 2015.

A world of ideas

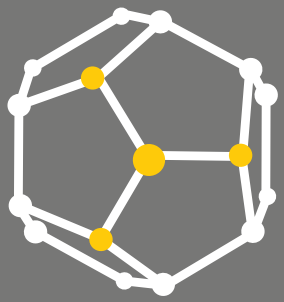
The continued success of our investments, which we manage ourselves and which fund all the work we do, means the Wellcome Trust intends to spend up to £5 billion over the next five years. Most of this money will still be used to support people who come to us with great ideas, but our increased budget is an exciting chance to expand the ways in which we work. In March 2015, therefore, we began to think about exactly how we could build on our past strengths, respond with speed and purpose to new challenges, and be more ambitious about the difference we can make in the world. We drew on the wisdom and expertise of our staff, the people we fund and international leaders in science, research and public engagement to analyse our organisation and the opportunities before us.

The result was a new strategic approach, which defines our philosophy and establishes a framework to support the work we want to do. Our philosophy starts from the fact that good health makes life better and the Wellcome Trust improves health by helping great ideas to thrive. Our framework sets out three complementary approaches to doing this: advancing ideas, seizing opportunities and driving reform.



Advancing ideas is our core activity: supporting people dedicated to discovery, creativity and innovation, people with great ideas to make health better. We know it works because we have achieved so much already by giving people the freedom to explore the most exciting possibilities they can imagine.

We will back ideas in any field of research related to health, and this approach will always account for the majority of what we spend.



Seizing opportunities means identifying times when a concerted intervention by the Wellcome Trust, alone or in partnership, could significantly accelerate progress in an area of critical need. It might involve harnessing an emerging technology or a new field of endeavour, or bringing together people and ideas with focused, intensive support.

We have identified four initial priorities for this approach, such as tackling drug-resistant infections, which threaten to undo the past century's success with antibiotics, and the development of vaccines for areas of unmet clinical need.

Driving reform is about changing ways of working so that more ideas flourish. Some practices enable ideas to reach their full potential – others get in the way. We will advocate for better practice, leading by example and campaigning for wider reform.

There are three priorities in this approach so far, including improving the systems that help translate science into better health.

Future opportunities

This strategic approach allows us to be more flexible and take more risks. We started in October with seven priorities – more will be identified, and each will have its own goals and timeframe. Not every effort will succeed, but those that do will transform lives.

A fundamental part of it, therefore, is listening to our partners and the wider community to identify new priorities and set the right objectives. We will use a range of means to engage people in this continual process, especially junior researchers and younger voices, who sometimes struggle to be heard.

One channel we are exploring is Frontiers meetings. These are designed to provoke, challenge and inform our thinking about the future of health, medicine, science and society. In September 2015, for example, we talked about collaboration across disciplines with a diverse audience, including early-career researchers with great ideas spanning different areas of science.

It is this type of discussion that we want to encourage in the future: open conversation inspiring new ideas and forging new collaborations – and a reminder that the future is just history waiting to be made.

Clare Matterson, Director of Strategy, Wellcome Trust

Mitochondrial donation

NANCY LEE

In the House of Commons on Tuesday 3 February 2015, a cheer rang out from the public gallery. Parliamentarians looked up in surprise. It's rare for them to witness immediate reactions from people their votes will affect directly. Those in the gallery had just watched MPs vote to make the UK the first country in the world to allow mitochondrial donation – which could allow hundreds of families to have healthy children.

> "EVERYONE PUT HEART AND SOUL INTO THE CAMPAIGN"

The energy our cells need is generated by mitochondria. Abnormalities in these tiny organelles, however, can cause heart problems, diabetes, muscle weakness, epilepsy and, in the most serious cases, death. Around 1 in 6,500 children are born with a serious mitochondrial disorder. There is no treatment and no cure – all doctors can do is try to manage the symptoms.

For many years, the Wellcome Trust has funded Professor Doug Turnbull and his colleagues at Newcastle University to research mitochondria. In 2010, I received an email from our press office, asking if I could meet with Professor Turnbull. He had a paper coming out in *Nature* and thought it might be controversial.

The paper showed that a new technique called pronuclear transfer had the potential to enable a woman at risk of passing mitochondrial disease on to her children to have a healthy, genetically related baby. This technique replaced faulty mitochondria from the mother with a donor's healthy mitochondria, and was controversial because the baby would inherit DNA from three people. But, like a similar technique (maternal spindle transfer) that researchers had been working on for the same purpose, it required a change in UK law to be used in patients.

So began a process of scientific reviews, public consultations and ethical debates. Colleagues across the Wellcome Trust worked with a range of stakeholders, including patients and their families through the Lily Foundation, to support our researchers. Our goal was to make it possible for mitochondrial donation techniques to be licensed in clinics and enable families to have babies free from mitochondrial diseases.

After winning in the Commons, there was one more vote to go: the House of Lords, three weeks later, but a late wrecking amendment was threatening to stop the legislation going through. Everyone put heart and soul into the campaign, doing media interviews, briefing peers on the issues, working so hard until that moment when suddenly nothing more could be done.

It paid off. The Lords also voted in favour of allowing the Human Fertilisation and Embryology Authority to issue licences for mitochondrial donation, and the law came into effect in October 2015. Now we are working to ensure that families who would benefit from these techniques can access them in the clinic.

It is not often that we at the Wellcome Trust get to meet people who will directly benefit from research we fund. Working with families affected by mitochondrial disease has made this an exhilarating and truly rewarding experience.

Nancy Lee, Senior Policy Adviser, Wellcome Trust

Vicky Holliday and her daughter Jessica, who has the mitochondrial disease Leigh syndrome. *Photography by Jo Metson Scott, commissioned for the Wellcome Trust*

Smart vision for the future

In August 2015, Indian company Remidio launched a portable device that takes high-resolution pictures of the retina at the back of the eye. Anyone can be trained to take pictures using the device, called Fundus on Phone, which then sends the images electronically to an ophthalmologist to look for early signs of abnormalities in the retina. Over 150,000 people have already been screened using the device.

India has many people with diabetes who are at risk of developing chronic eye conditions, including retinal abnormalities that, if untreated, could lead to blindness. In pilot programmes, 13 per cent of people with diabetes who were screened were found to have retinal conditions that required follow-up or treatment.

Developed with funding from the Wellcome Trust's Affordable Healthcare in India scheme, Fundus on Phone could increase the number of people being screened, many of them for the first time. This could potentially save the sight of thousands in India and around the world by enabling decentralised, non-specialist eye screening.

Diana Tay, Business Development Manager, Wellcome Trust

The Fundus on Phone device. *Photography by Remidio Innovative Solutions Pvt Ltd*

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150,000

Over 150,000 people have been screened using Fundus on Phone

Vaccine prevents severe diarrhoea in Malawi

Most cases of severe, acute diarrhoea are caused by rotavirus, which kills more than 450,000 children under five in the world each year. Rotavirus vaccines have been proven to work in clinical trials, but no one had assessed their real-world effectiveness in sub-Saharan Africa. A team from the Malawi–Liverpool–Wellcome Trust Clinical Research Programme set out to evaluate the vaccine as used in Malawi.

There is always a question over how well the performance of a vaccine in clinical trials translates into practice. Trial participants are generally more engaged with the healthcare system than most people, and outside of a trial there can be difficulties with storing and delivering vaccines.

Malawi is also a low-income country with high rates of malnutrition and exposure to HIV. We wanted to know if the rotavirus vaccine was actually reducing childhood infections in this context.

Malawi has always been proactive in implementing vaccine policies. Government ministers and non-governmental organisations worked closely with us, both on the logistics of doing the research and to help make sure our findings would be relevant.

In the end, we found that rotavirus vaccination reduced the risk of severe diarrhoea by 64 per cent, confirming that it is a highly effective – and cost-effective – way to prevent life-threatening disease for many children in Malawi.

Naor Bar-Zeev, Senior Research Fellow, University of Liverpool

Getting better at getting better

Organisations like the Wellcome Trust support scientific discoveries to improve health. But patients may not benefit from these innovations – or even reliably receive care consistent with good practice – if health systems are unable to deliver.

The example of the World Health Organization's surgical safety checklist shows just how hard it can be to implement new interventions. Many countries made the checklist mandatory after a study suggested it improved outcomes.

But attempts to implement the checklist were not always optimal. Sometimes surgeons and nurses were trained separately, for example, and a tool intended to eliminate unhelpful hierarchies in the operating theatre actually deepened them. The checklist alone could not solve many safety problems: whole systems needed to be redesigned.

I have a Wellcome Trust Senior Investigator Award to apply sociological insights to improving the quality and safety of patient care. I'm working with colleagues and collaborators across various disciplines in several countries.

Our aim is to understand what it takes to get interventions to work and whether and how they can be scaled up from initial promising results. Already, we are persuading people – surgeons, infectious disease specialists, policy-makers and others – of the value of our approach and recommendations. It's proof that social science can lead to practical actions that help more patients to benefit from advances in medicine.

Mary Dixon-Woods, Professor of Medical Sociology, University of Leicester

Diagnosis revolution

Babies with diabetes used to have to wait on average, more than four years after their initial diagnosis to be tested for the genetic cause of their condition. Even then, they would be tested only for one possible cause, based on the symptoms they had at the time. Today, they can be tested for all 22 known genetic causes of diabetes as soon as they are diagnosed. This means doctors have better information about how each baby's condition is likely to develop in the future, and what will be the best treatment from the start.

In July 2015, Professor Andrew Hattersley and colleagues published results from more than 1,000 babies who have had these tests over the past ten years. In 40 per cent of cases, the cause was a genetic mutation that meant the babies could stop having insulin injections and be treated with sulphonylurea tablets instead. Identifying the right treatment early can avoid more serious complications from diabetes in childhood and later in life.

These tests were all done at the University of Exeter Medical School, where years of Wellcome-funded research on the genetics of diabetes in babies identified the most common genetic mutations responsible. Understanding the biological role of one of the mutations led directly to the development of sulphonylurea as an alternative treatment in those cases. The Exeter team now get samples for testing sent soon after initial diagnosis from across the world.

This is not about using genetics to confirm a diagnosis; it is about using genetics to give a more precise diagnosis, earlier than ever used to be possible, and it has transformed healthcare for these young patients.

Michael Regnier, Science Writer, Wellcome Trust

A performance of *Brainstorm*.
Photography by Richard H Smith

Neuroscience on stage

Who better to explore the science of the teenage brain than teenagers? That was the idea behind Brainstorm, a play created by Islington Community Theatre with support from the Wellcome Trust. In 2015, Brainstorm was performed at the Park Theatre in London and then at the National Theatre. Cast member Michael shares his experience:

We want people to know that teenage brains are not broken, that it's normal to be a teenager and we just have different characteristics growing up. One person said afterwards they wished they'd known that when they were a teenager. Even our parents never really understood these things, and one of the effects for the cast has been that we have improved relationships with our parents. It's been reassuring for them to understand what we've learned.

At first, the science seemed like an obstacle to me. Then, during a five-day residential making the show, the neuroscientist we were working with made us understand the purpose of it and how it could help.

I'm 15 now and have been involved with the show for two or three years. I realised early on that the commitment had to be 100 per cent. That's what has made the show as good as it is, and it has helped me, too, and made me want to pursue theatre as more than a hobby.

Walking out on the National Theatre stage for the first time was surreal and brilliant. I can't wait to be back there in spring 2016 to do it all again.

Michael Adewale, Islington Community Theatre member

Ebola vaccine shows promise

I'm not sure any of us really thought that we would see a vaccine for Ebola being 100 per cent effective in a clinical trial this year, but that was the news from Guinea in August 2015. This and other vaccines in development are now being assessed across Africa to build on this incredible achievement.

The Wellcome Trust moved really quickly on this, funding a safety trial and then the efficacy trial within eight months. It took a lot of effort and goodwill and has been a truly global collaboration. And it's so rewarding to be involved in something this important.

Charlie Weller, Senior Portfolio Developer, Wellcome Trust

A visualisation of antibodies being activated by the Ebola vaccine. *Photography by Catherine Losing and set design by Sarah Parker, commissioned for the Wellcome Trust*

Hearing the Voice

CHARLES FERNYHOUGH

If you hear someone's voice, it's natural to listen. But what if there was no 'someone' around? What if that voice was in your head? Would you listen? And would anyone listen to you?

We tend to think of voice-hearing as one thing, usually a bad thing: mental illness, psychosis, schizophrenia. But when you start listening to people who hear voices and studying representations of voice-hearing in literature and research, you find it takes many forms.

> "THEN THERE'S THE MAGIC WHEN THE TWO MEET ON EQUAL TERMS"

Thinking about voice-hearing and inner speech, it became clear to me that you can't make sense of such human experiences just through impulses in the brain. As soon as we experience something we start to try to make sense of it, which becomes an intrinsic part of the experience. So my Durham colleagues and I wanted to come at voice-hearing from every angle – psychological, philosophical, literary, neuroscientific, spiritual, theological… anything that would help make sense of this phenomenon.

We came to the Wellcome Trust in 2012 to gauge their interest in our work and were given a three-year grant to see if our approach was practicable. It turned out it was, and this year the research team – around 20 of us, along with a wider group of national and international collaborators – got one of the first Wellcome Trust Collaborative Awards to take our Hearing the Voice project even further.

Illustration by Merijn Hos, commissioned for the Wellcome Trust

Our success has come precisely because we have interwoven so many disciplines. The humanities make our science better, and the sciences enhance our humanities research. And then there's the magic that happens when the two meet on equal terms.

For example, a psychologist and a narratologist are analysing data on how readers experience characters' voices in books. Every reader is different, so they are creating a new analysis of how these literary voices work for and within us.

We are gathering and generating all this knowledge and wisdom so that we can make a difference to people who hear voices. We couldn't do it without them. Without hearing their voices. And hearing about their other voices – how distressing they can be, but also how nourishing, even funny.

Hearing voices does not mean you are schizophrenic. It does not mean you are suddenly a danger. Such perceptions are stigmatising. They isolate people who start hearing voices – often teenagers and young adults – adding to the anxiety they feel because they share these preconceptions, too.

A lot of our work is aimed at helping people who are distressed and struggling with their voices. But everyone's experience is different, and we want to open up a space in which every voice can be heard.

Charles Fernyhough, Professor of Psychology, Durham University

Transforming research in Africa

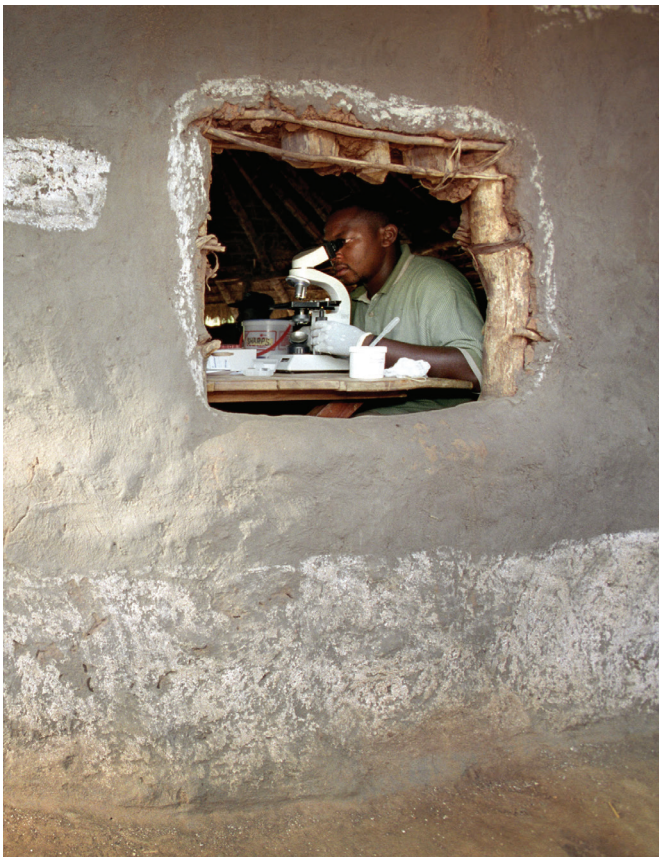
In September 2015, I was in Nairobi, Kenya, to celebrate seven new grants that marked the beginning of a huge and permanent shift in the way African science is funded.

The Wellcome Trust has long invested in health research in sub-Saharan Africa. We have supported excellent science through our African Institutions Initiative, the genomics programme H3Africa, and our Major Overseas Programmes in Kenya, Malawi and South Africa.

Our new DELTAS Africa programme – which is co-funded with the Department for International Development and which made those seven grants in September – establishes world-class research environments at African universities, with a focus on training the next generation of excellent researchers.

What it also does is shift the centre of gravity for the leadership and management of African science firmly into Africa itself.

From 2016, the DELTAS Africa budget – £46 million over five years – will be managed by the newly launched Alliance for Accelerating Excellence in Science in Africa (AESA). This has been created by the African Academy of Sciences and the New Partnership for African Development under the auspices of the African Union.



Sven Torfinn/Panos

46m

The DELTAS Africa budget is £46 million over five years

We expect AESA to transform science in Africa, working with national governments to increase support and funding for research. This will enable internationally competitive researchers to lead and conduct the most locally relevant research to improve health across Africa.

Simon Kay, Head of International Operations, Wellcome Trust

International insights for public health

In October 2014, INDEPTH published a dataset of 110,000 deaths across 13 countries in Africa and Asia. It is an unprecedented insight into people's health, including the variable burdens of infectious diseases and childhood mortality.

The INDEPTH Network is based in Accra, Ghana, but encompasses dozens of health and demographic surveillance system sites in low- and middle-income countries. Supported by many organisations, including the Wellcome Trust, Sida and the Hewlett Foundation, we were uniquely placed to pull together data on causes of death collected by hundreds of researchers over the years.

For each death, a field researcher conducted a standard verbal autopsy with a relative of the person. Information from this structured 15-minute interview was then processed to identify the likely cause of death.

This allows us to see patterns, such as the decline in HIV/AIDS as a cause of death at a site in rural South Africa, probably as a result of public health programmes taking effect. It also highlights areas for concern, such as childhood drowning in Bangladesh and high murder rates in eastern and southern Africa.

The entire dataset has been made freely accessible on the INDEPTH Data Repository (indepth-ishare.org). It is vital information for researching and supporting public health systems.

Osman Sankoh, Executive Director, INDEPTH

Brain power

A world-class group of neuroscientists hope to make a fundamental leap forward in our understanding of the cerebral cortex, the part of the brain responsible for human intelligence. With Wellcome Trust support, complementary approaches refined in their labs will be integrated with new techniques to investigate the cortex on many levels, from individual cells to its overall organisation.

Led by Kenneth Harris at University College London, the team will first classify different types of cell in the cortex, then record their activity and relate their interactions to behaviour and cognition. It's a really exciting endeavour, and could lead to an unprecedented understanding of our brains.

Giovanna Lalli, Science Portfolio Developer, Wellcome Trust

First genetic clues to depression

Depression is the second most common cause of ill health in the world, yet we know so little about it. Lots of environmental and biological pathways are involved, which makes finding any genes linked to depression very difficult.

This year, however, the CONVERGE consortium reported the first genetic markers of depression. We compared the genomes of more than 5,000 Chinese women, most of whom had severe melancholia, with a control group. We did everything possible to exclude potential factors other than genetics, which is almost certainly why our study identified two genetic sequences linked to depression where others had failed.

Neither of the sequences we identified are genes, so we will now have to investigate their biology – what do they do, and how might that contribute to depression?

CONVERGE is a collaboration between researchers at the Wellcome Trust Centre for Human Genetics in Oxford in the UK, the Virginia Institute for Psychiatric and Behavioral Genetics in the USA, and the Beijing Genomics Institute in China, as well as many Chinese hospitals who helped to recruit all our participants.

Working in China posed challenges – it is such a different culture from the West. But China has a very integrated health system and our partners were outstandingly open and helpful, which made the project possible. Plus, we shared a conviction that this work would benefit us all by getting a handle on the biology of this poorly understood but devastating disease.

Jonathan Flint, Professor of Molecular Psychiatry, Wellcome Trust Centre for Human Genetics

80%

Young people spend up to 80 per cent of their waking hours outside of school

Learning about science outside school

How many times did you visit a science museum when you were a child? Perhaps you saw some of the myriad films and plays that have scientists as characters? Maybe you were lucky enough to go along to a 'pop-up science shop'?

Young people spend up to 80 per cent of their waking hours outside of school, meaning that they can have many opportunities to engage informally with science. It's partly why activities funded by our Engaging Science department help young people of all backgrounds to engage with and learn about science. A challenge for us is to understand the value of these experiences.

Through Science Learning+, we have funded social scientists and those who engage different audiences with science to collaborate and start exploring what participants in informal science experiences might take away from them. The initiative is a collaboration with the National Science Foundation in the USA and the Economic and Social Research Council in the UK.

The first phase of Science Learning+ provided funding for 11 research groups to develop ideas to explore bigger questions. In summer 2016 we will fund five large projects that will really probe the impacts of informal science experiences, how we can measure these impacts, and how they complement the wider education ecosystem.

Mat Hickman, Programme Manager, Education and Learning, Wellcome Trust

Shared heritage

The Wellcome Library is in the middle of a major digitisation project. In 2014, we started to digitise over 60,000 historical medical texts. These 19th-century books and pamphlets, contributed by us and nine other research libraries around the UK, form part of the Medical Heritage Library collection.

Created by a consortium of North American research libraries in partnership with the Internet Archive, the Medical Heritage Library makes all its content available online under an open access licence. The Internet Archive currently has 15 staff at the Wellcome Library, digitising up to 900,000 images a month. The Higher Education Funding Council for England contributed £2.5 million to the UK-based project through Jisc, while we committed £1.5m from our own digitisation fund. The goal is to digitise 15m pages by April 2016, and we are well on track.

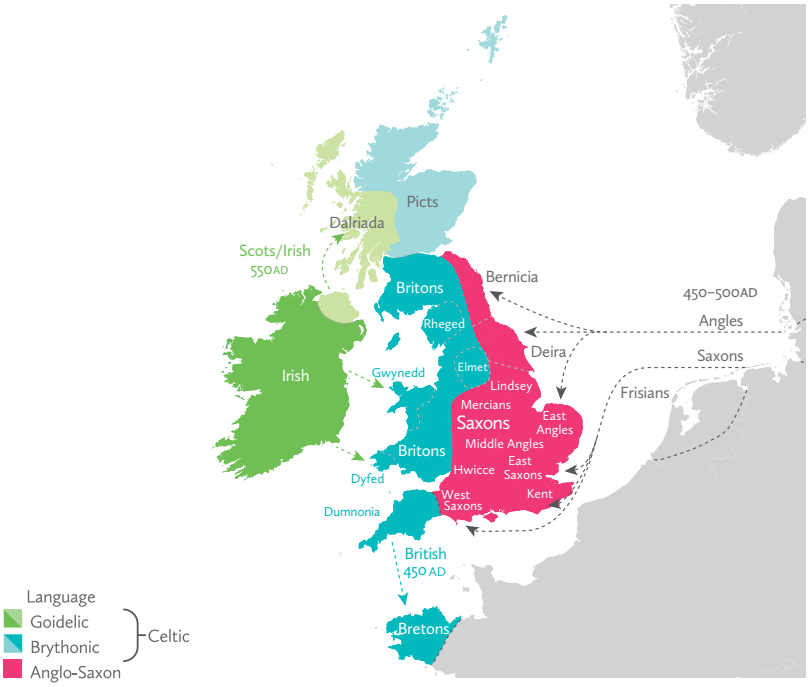
Over 30,000 titles were made available this year on the Internet Archive and the Wellcome Library website. This is providing a valuable corpus of historical materials on a wide range of topics related to health.

Christy Henshaw, Digitisation Programme Manager, Wellcome Library

Photography by Jill Todd

Tracing genetic footprints across the UK

PETER DONNELLY



Population groupings in 600 CE, and major migrations.

Who are the British and where do they come from? Thanks to modern genetics, we can now see in exquisite detail the origins of the UK's population and the history of British migrations.

In March 2015, my colleagues and I published an analysis in *Nature* showing that although all today's Britons are ultimately descended from immigrants, many have very local roots stretching back over a thousand years.

The People of the British Isles study, led by my colleague Sir Walter Bodmer, recruited volunteers from rural areas across the UK. With researchers now based at University College London and the Murdoch Childrens Research Institute in Australia, we looked at the genomes of 2,000 people whose four grandparents were all born within 80 km of each other. This gave us a fine-grained genetic map of late Victorian Britain, before the upheavals of the 20th century. To understand historical migrations, we also compared the details of this map with a genetic analysis of 6,000 people from across Europe.

To do all this, we had to use cutting-edge statistical techniques, including two algorithms – known as fineSTRUCTURE and GLOBETROTTER – that were developed by some of our team members. These allowed us to analyse DNA differences at over 500,000 points in the genome, then to separate our sample into genetically similar groups. The genetic groups we found revealed striking geographical patterns, and allowed us to connect European populations with British ones.

We found that the Romans, Vikings and Normans left little genetic trace; whatever their social and political influence, they did not breed with the natives in large numbers. The one big exception to this was in the Orkney islands off the north of Scotland. There, we found that a quarter of people's DNA came from Norwegian ancestors, Vikings who settled the islands from the ninth century.

The Anglo-Saxons did integrate in substantial numbers. Their migrations, during the fifth, sixth and early seventh centuries, permanently changed British DNA. They didn't replace the existing populations but married and bred with them, and their descendants are a genetically similar group, making up the bulk of the population of eastern, central and southern England.

There is not, though, a single 'Celtic' population. We did see distinct genetic groups

in the traditionally Celtic regions of the UK, but these groups were quite different from each other. While we found a clear genetic boundary where Cornwall and Devon meet, the modern Cornish are genetically much closer to the rest of England than to other Celtic groups. In Northern Ireland we found two populations: one shared with western and northern Scotland, the other with southern Scotland and northern England.

In Wales, the north and south differ about as much from each other as central and southern England differ from northern England and Scotland. But we did find in Wales the strongest traces of Britain's original population: the settlers who came here after the last Ice Age, nearly 10,000 years ago.

And, intriguingly, outside Wales, we found the genetic footprints of another early migration – one previously unknown to historians and archaeologists. We can only speculate who these migrants were, but it appears that they probably arrived between those very first settlements and the Roman invasion, and the analysis suggests that they have other descendants in modern France.

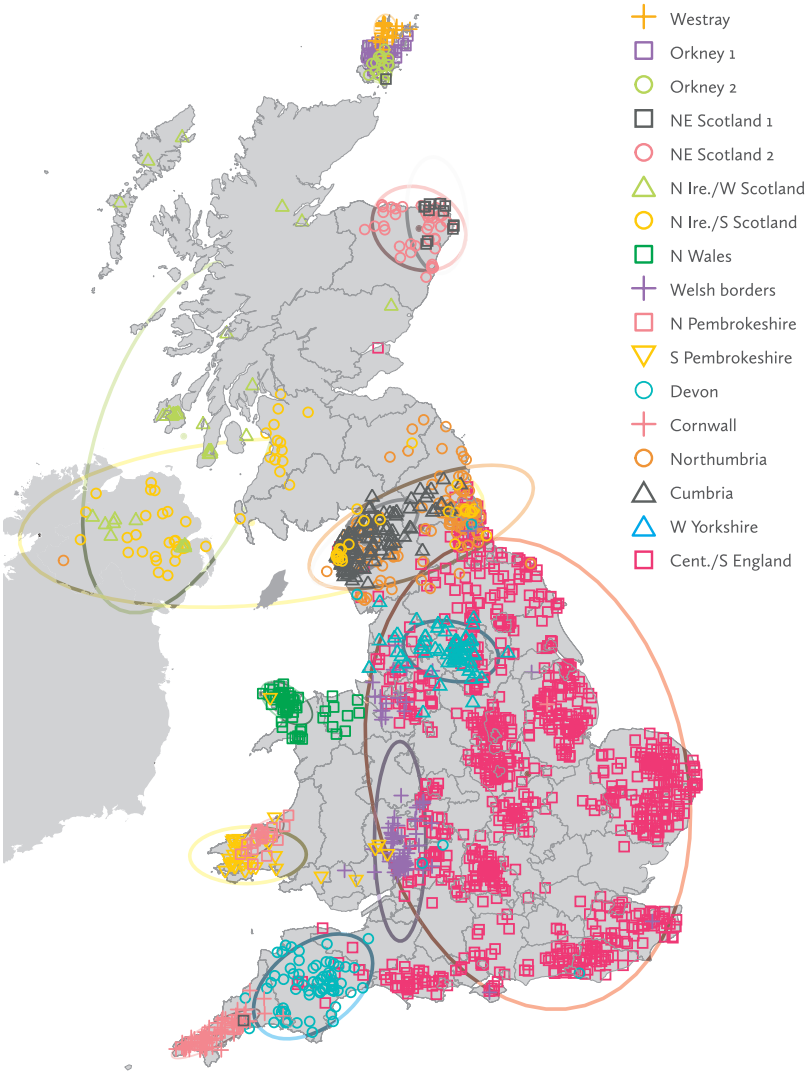
Perhaps the biggest story, though, is one not of movement but of stability. The 19th-century genetic maps are strikingly similar to maps of the tribal groupings of the late sixth century, towards the end of the Anglo-Saxon influx. For example, a genetic cluster in West Yorkshire corresponds with the territory covered by the kingdom of Elmet, which fell in the early seventh century. Another cluster coincides with the kingdom of Bernicia, which was absorbed into Northumbria around the same time, and a cluster in Cumbria marks the kingdom of Rheged, which was annexed in the eighth century.

So, through more than a millennium of cultural, political, military and technological upheaval, generation after generation lived their whole lives, raised children and died in the same region they were born. The rural Victorians lived – and many of us still live today – among early medieval tribal kin.

This unprecedented insight into British population history is fascinating, but our work, supported by the Wellcome Trust, has broader implications. By painting such a highly detailed picture of population genetics – and by developing new statistical techniques along the way – we have created a tool that other researchers can use.

Patterns of disease vary across the country. To find out why, and then how to treat and prevent these diseases, it helps to know how much of this variation is genetic. Now we have established a genetic baseline for the population, this task may become that much easier. Rediscovering the UK's past could help to give the country – and the rest of the world – a healthier future.

Peter Donnelly, Professor of Statistical Science and Director of the Wellcome Trust Centre for Human Genetics, University of Oxford



The modern genetic clusters that the study identified correspond well with the borders of medieval tribes and kingdoms.

Both figures adapted by permission from Macmillan Publishers Ltd: Nature. Leslie et al. (2015). The fine-scale genetic structure of the British population. Nature 519, 309–314. © 2015.

Sex and violins

Wellcome Collection emerged from a year of development in spring 2015 bigger and bolder, to great acclaim. Our new and expanded galleries have already supported ambitious exhibitions and events, demonstrating Wellcome Collection's continued ability to intrigue, inspire and surprise, and attracting more visitors this year than ever before.

The inaugural exhibitions, *The Institute of Sexology* and *Forensics*, explored provocative aspects of human experience and were accompanied by installations by young artists in our new Studio.

Through the summer, visitors had the chance to participate in Alice Anderson's Travelling Studio and share their secrets in Neil Bartlett's reimagined sex survey. And, as the season turned, BBC Radio 3's residency 'Why Music?' filled the building with music and new visitors.

Holly Story, Assistant Media Officer, Wellcome Collection

Inspired by the ideas of identity raised in *Forensics: The anatomy of crime*, a group of artists from Leyton Sixth Form College produced a body of work using elements of the forensic process. *Photography by Edmund Clark*

The Big Data Virtual Reality Challenge

KARL MADDIX, REBECCA WILSON AND HUGH GARNER

Virtual Reality (VR) is not just a gamer's plaything but an exciting new technology with potential applications in almost every sector. That's why the Wellcome Trust's Big Data VR Challenge was so exciting. We knew they'd worked with the games industry to engage more people with scientific research – now they were challenging us to think about new roles for VR in research itself, particularly in handling big datasets.

We were chosen to be finalists in the competition, which had teams from Australia, Canada, Denmark and us in the UK, all working with the latest VR hardware. Our company, Masters of Pie, joined up with our friends at Lumacode to form team LumaPie, and we began working with researchers at the Avon Longitudinal Study of Parents and Children to augment the analysis of their ever-increasing data.

VR is still in its early stages, meaning almost anything we build is in uncharted waters. Our approach this time was to complement human analytic skills, such as spatial, colour, pattern, size and movement recognition.

We were thrilled to win, and we hope to develop our prototype right through to a commercial product. But all the approaches that the teams came up with were unique and were reported on by *New Scientist*, the BBC and a host of tech and gaming publications.

The problem of handling big data is universal. This challenge allowed us to think big and really show how innovative we could be.

Karl Maddix, Masters of Pie

We both work with ALSPAC – the Avon Longitudinal Study of Parents and Children. It has been charting the health of 14,500 families in the Bristol area since the early 1990s and has generated a database of surveys and samples that grows every year. Our teams' roles are to think about how to collect, look at, format, work with and communicate all that data.

When we began to work with LumaPie, we had to understand what VR could do and they had to understand what our data could be. They got to grips with the complexity of our datasets really quickly.

For us, the breakthrough came when what had essentially been doodles on napkins turned into a prototype. Putting the VR headset on, it hits you straight away how easy it is to identify patterns in the data. Moving your head even slightly is enough to get a sense of the distance between data points in a way that just doesn't work in static, 2D graphs.

The competition gave us the core of a useful system, and we definitely want to keep on exploring it and get to a usable piece of software. At the moment, we can only convey the structure of the ALSPAC cohort data to other researchers by using complex files of metadata and word-of-mouth. A VR approach with flexible search and selection would be a major leap forward.

Rebecca Wilson and Hugh Garner, University of Bristol

Illustration by Melvin Galapon, commissioned for the Wellcome Trust

Bringing MRI within reach for sick babies

SARAH HARDY

The neonatal intensive care unit is home to a hospital's most vulnerable patients: premature and full-term babies with serious health conditions. For most of them, 70 per cent, the biggest risk is brain injury. If they were adults, magnetic resonance imaging (MRI) would be routinely used to look at what's going on inside their heads. But the risks of taking a sick baby through the hospital to the radiology department often rule out MRI as an option, so staff rely on ultrasound instead.

> "IT'S GREAT TO SEE YEARS OF TEAMWORK BEGINNING TO PAY OFF"

Ultrasound is portable, cheap and simple to use, even with very sick babies, but it might not be revealing as much information as an MRI scan would. No one knows, however, because it is hard to directly compare the two. Many doctors who work with babies have thought about bringing MRI scanners onto their wards. But these huge, noisy machines are not usually practical for the neonatal unit.

In 2011, the Wellcome Trust's Innovations division made an award in collaboration with GE to develop, create and install a very small but powerful 3 Tesla scanner in the heart of a neonatal intensive care unit.

Professor Ellen Grant in Boston, USA, and Professor Paul Griffiths in Sheffield, UK, have been working with a team of specialist engineers, radiologists, MR technologists, designers and nurses. As well as doing groundbreaking work to reduce the size of the magnet and adapt the coils and electronics that make the scanner work, they have had to understand how neonatal medicine operates.

Making the machine as quiet as possible and monitoring the temperature were critical. They also had to think about how to move a vulnerable baby from an incubator to the scanner, and how to keep monitors and IV drips connected while scanning in a room where no metal would be allowed.

But they cracked the major challenges, and in June 2015, the team in Boston scanned the first baby using the new prototype system. A second prototype will be installed in Sheffield shortly. GE will use the results from these two evaluations to decide how best to develop such a product in the future.

It's great to see years of clinical partnership and teamwork beginning to pay off. A lightweight and compact system with a high field strength reduces the challenges that come with placing the scanner closer to babies in neonatal units, without compromising on clinical capability. It means high-quality research can now be done to assess whether MRI gives more information than ultrasound to clinicians looking after this special group of patients. And if MRI became routine in neonatal units as a result, more research could then be done to better understand the development and needs of premature babies, as well as transforming neonatal intensive care.

Sarah Hardy, Senior Business Analyst, Wellcome Trust

Kerry Hughes was inspired by the age-old tradition of knitting a wool hat for a newborn to create this fragile knitted brain. *Photography by Aaron Tilley and set design by Kerry Hughes, commissioned for the Wellcome Trust*

Our Planet, Our Health

Malnutrition, extreme weather, infectious disease outbreaks, shortages of safe urban housing – such challenges show that the health of the population is inextricably linked to the health of the planet. But there is a poor ecological fit between the planet's resilience and what we ask of it.

In September 2015, the Wellcome Trust launched Our Planet, Our Health. This is a £75 million initiative to build understanding of the complex links between the environment and our long-term health. Our aim is to develop a stronger evidence base for people and governments to make informed decisions.

At the launch, as well as opening a call for proposals to establish ambitious research programmes, we announced ten new pilot projects involving collaborations of researchers across the globe from a range of disciplines.

For example, Indonesian and US scientists will carry out research with nearly 30,000 people affected by the 2004 Indian Ocean tsunami. They will assess the long-term health effects of environmental disasters. And a project in the Netherlands will investigate the potential of duckweed as a protein source. Duckweed is the world's smallest flowering plant and one of the fastest-growing, and it has around ten times the protein content of soya.

Saskia Heijnen, Research Analyst, Wellcome Trust

Photography by Mike Kock

£75m

Our Planet, Our Health is a £75 million initiative to build understanding of the complex links between the environment and our long-term health

Dharavi Biennale

Art is a powerful talking point, which makes it a great way to get people talking about their health, too. In February 2015, a vibrant art and health festival transformed Dharavi, a Mumbai slum, and got the community talking about their health and related cultural, economic, environmental and political issues.

The theme of the project was recycling, using artworks made from recycled materials to explore subjects such as children's diets or violence against women. I was in Mumbai for only two days of the festival but it was enough to see the immense power of this project to portray and address the complex lives of Dharavi's residents.

Helen Latchem, International Engagement Adviser, Wellcome Trust

New malaria prospect

The need for new antimalarial drugs is more urgent than ever before, with strains of the malaria parasite emerging that are resistant to our best current drugs. So it was exciting when, in June 2015, researchers published details of a new compound (called DDD107498) that kills the parasite in mice.

The work was a collaboration between the University of Dundee's Drug Discovery Unit and the Medicines for Malaria Venture, and was supported by the Wellcome Trust. Although there is a lot to do to develop this compound into a drug for patients, it is a promising new prospect in the hunt for new malaria treatments.

Michael Chew, Science Portfolio Adviser, Wellcome Trust

The origins of cancer

Cancer begins when a cell acquires genetic mutations that remove its inbuilt controls. This understanding came from looking at genes in cancer cells and working backwards. With the technology we had, it was impossible to watch the process going forwards and see how those mutations really developed.

This year, I was part of a team at the Wellcome Trust Sanger Institute that used 'ultra-deep' genetic sequencing to unravel the extent of mutations in healthy cells. Hoping to shed light on the earliest steps towards cancer, we studied over 200 biopsies of normal eyelid skin from four healthy people.

Although we expected to see some mutations caused by a lifetime of ultraviolet radiation from sunlight, we were surprised to see that an average skin cell carried 20,000 mutations, and a quarter of them had already acquired a first 'driver' mutation, strongly associated with cancer.

It was surprising, but it fits with our understanding of cancer's origins. Although mutations are more common than we thought, the chances of having enough driver mutations in a cell to start a cancer are still relatively low, and the presence of driver mutations does not necessarily indicate cancer. This means we should be cautious about developing any treatment that targets cells with such mutations, as this may damage a significant number of healthy cells as well.

Iñigo Martincorena,
EMBO Postdoctoral Fellow,
Wellcome Trust Sanger Institute

*****
20,000
An average skin cell carries 20,000 mutations

Threads of inheritance

In my lab, we study chromatin, a structure that packages DNA inside cells by wrapping it like thread around 'spools' of proteins called histones. The histones can be modified by adding or removing small chemical marks, which either tighten or loosen the thread.

Where the chromatin is tightly wound, genes are inaccessible and inactive. Where it is looser, genes are accessible and can produce the components that the cell needs to function. Different patterns of activation give rise to different types of cells, which makes histone marks an important type of 'epigenetic' regulation.

Genes get copied when a cell divides – that's how we inherit traits from our parents – but it is less clear how the epigenetic pattern of active and inactive genes is carried over, and whether histone marks are maintained or erased. It is hard to examine this in human cells because other mechanisms that regulate genes interact with histone marks as well.

Pauline Audergon, a PhD student in my lab, looked at a particular histone mark in yeast cells, which are less complex. She added this mark to a specific histone to inactivate a particular gene. Then, as the cells divided, this mark was copied and passed on, meaning the gene remained switched off in subsequent generations.

Now we know that histone marks can be heritable. This could well be the case in people, too, which will be relevant to studying how various epigenetic processes relate to health and disease.

Robin Allshire, Wellcome Trust Principal Research Fellow, University of Edinburgh

Eliminating dengue disease

Photography by Wellcome Images

During the last 12 months the Eliminate Dengue Program, co-funded by the Wellcome Trust since 2014, has continued to increase the number of sites around the world where *Wolbachia*-infected mosquitoes have been released into the environment. These infected mosquitoes are far less able to transmit viruses to people, and early results from these experimental releases are very encouraging, with no locally acquired dengue cases in any of our release areas to date.

In October 2014 we commenced our first city-wide trial in northern Australia, a key step in scaling up our method for low-cost, large-scale application in dengue-endemic cities around the world.

The next goal of our research is to evaluate the impact of our approach by directly measuring the reduction of dengue in large randomised trials. In preparation we are undertaking baseline studies in selected areas to inform trial design. The first stage of this research began in Nha Trang, a coastal city of 400,000 people in Vietnam. Our team has begun collecting information on population mobility, dengue transmission and local mosquito population dynamics.

This will help us design trials of our *Wolbachia* method that will run over the next few years. The results of these studies will hopefully show that this approach can significantly reduce the burden of dengue disease for affected communities.

Scott O'Neill, Program Leader,
Eliminate Dengue

Innovation with impact

STEPHEN CADDICK

Scientific innovation has transformed our understanding and treatment of disease in recent decades. Millions of lives have been improved by the emergence of new classes of drugs such as biologics, vaccines and small molecules, and technological advances such as genomics and imaging have revolutionised clinical diagnosis and intervention. Overall we have seen a dramatic improvement in life expectancy for the majority of the global population.

> "WE HAVE TO ASK OURSELVES: WHAT MORE MUST WE DO?"

But the world is changing, and issues of population growth, ageing, climate change, pandemics and urbanisation offer increasingly complex contexts in which to further improve human health.

We can be optimistic, however, that those engaged in research will continue to deliver possible solutions – even to seemingly impossible challenges. From precision medicine to health informatics, from proteomics to digital health – we can have every expectation of further transformation in the decades to come.

And, of course, new technology will continue to play a critical role in driving medical innovation. Our role at the Wellcome Trust is to support the people developing, testing and applying new ideas, but also to create an environment for change, where great ideas are recognised, nurtured and put into action.

Focused but flexible

No one can predict where the next big disruptive technology might come from – but perhaps we might expect that it will originate from people working far from health. And so, in the future, I'd like to see more people from different disciplinary backgrounds encouraged to work in cross-disciplinary teams and create solutions to the problems we face. Perhaps we need to look at what is happening now in areas such as artificial intelligence, for example, to see how they might enhance our biomedical research capacity and speed up the path to innovation with impact.

I am extremely grateful to my predecessor, Ted Bianco, who established the Wellcome Trust's Innovations division and oversaw the development of a team willing to focus on the early-stage gap between discovery research and commercial application. At that time few organisations were able to do that, and the Seeding Drug Discovery, Health Innovation Challenge Fund and Affordable Healthcare in India schemes have enabled us to support dozens of exciting projects through that early stage.

In all, we have supported hundreds of successful projects, with some 30 products

The Fundus on Phone device being used to check a patient's retina. *Photography by Remidio Innovative Solutions Pvt Ltd*

developed and a similar number in the clinic. Just one example from India this year: a new product that uses mobile phone technology to bring retinal screening to thousands of people who just don't have access to an ophthalmologist (see page 8). With the support this device received from the Wellcome Trust, it has already been used to test 150,000 people who would never have had that opportunity. People with diabetes are at particular risk of serious eye problems and blindness. In pilot programmes using the new device, 13 per cent of people with diabetes who were screened were found to have conditions that needed treatment or follow-up investigation by a specialist. Most of these conditions would not otherwise have been detected until it was too late.

Such is the power of technology in healthcare, but I'm worried that many opportunities go unnoticed or bring change too slowly. So we have to ask ourselves: what more must we do?

Impatient, not hasty

The Wellcome Trust has amazing resources. We can be ambitious and support the most radical and transformational technologies. We can afford to invest patiently, act at scale and bring together the right people to help enthusiastic entrepreneurs realise the broadest benefits from their ideas. With our new strategic framework in place (see page 4), we will be able to continue that support for others while also starting to use more of our resources to pursue progress more vigorously and make change happen faster.

So 2016 is going to be an exciting year. We will be seeking advice on our plans, relying – as we have always done – on the wisdom, energy and creativity of people and organisations around the world to help us choose the right approach.

If we are to harness the opportunities that science and technology offer to address the challenges of global health, then innovation with impact is essential. No single organisation has the capacity to achieve this vision on its own, but the Wellcome Trust is uniquely placed to lead the changes necessary to enable people and organisations to turn the excitement and promise of discovery into innovations that will change the world.

Stephen Caddick, Director of Innovation, Wellcome Trust

The Wellcome Trust's work is funded from our £18 billion investment portfolio.

Funding and achievements

1,227
Total grants awarded

57
Countries receiving funding (38 directly, 19 indirectly)

573,848
Wellcome Collection visits

158
Fellowships awarded or renewed

£474m
Venture capital finance secured by grantholders for commercialisation of R&D

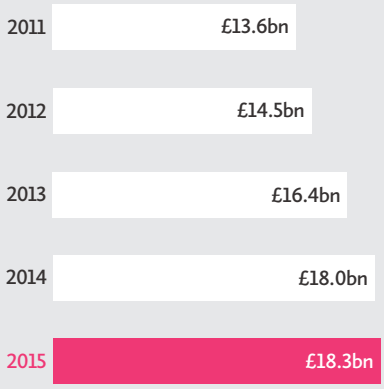
6,268
Scientific research papers associated with the Wellcome Trust
(Published in calendar year 2014, indexed on PubMed and in Thomson Reuters databases)

Key financials at a glance

Investment assets net of bond liabilities

£18.3bn

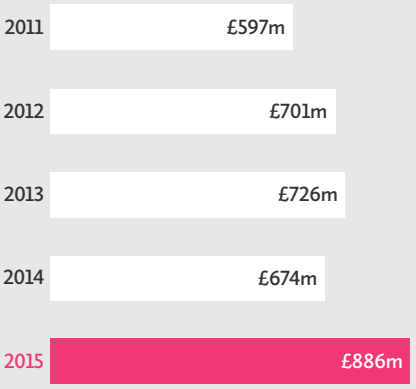
As at 30 September.



Total grant funding and direct charitable activities

£886m

For the year ended 30 September.



Financial summary
Our ability to support research and other charitable activities depends on the success of our investment portfolio. We invest globally across a very broad range of assets and strategies. In 2014/15, we were pleased that our investment portfolio recorded a total return of 6%.

We have returned a total of 45% (annualised 13%) over three years and 127% (annualised 9%) over ten years to September 2015. Since the inception of our investment portfolio in 1985, it has provided a total return averaging 14% a year.

Our annual grant-making budget is set by reference to a three-year weighted average of our portfolio's value in order to smooth the effects of short-term volatility.

For more details, see our *Annual Report and Financial Statements* at wellcome.ac.uk/annualreport.

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As at December 2015

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We are grateful to the many researchers and members of Wellcome Trust staff who helped to produce this volume, everyone who agreed to be reviewed, and everyone who gave us permission for their images to be used.

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Wellcome Trust

The Wellcome Trust is a global charitable foundation dedicated to improving health. We support bright minds in science, the humanities and the social sciences, as well as education, public engagement and the application of research to medicine.

Our investment portfolio gives us the independence to support such transformative work as the sequencing and understanding of the human genome, research that established front-line drugs for malaria, and Wellcome Collection, our free venue for the incurably curious that explores medicine, life and art.

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