Wellcome Science Review 2020

Contents

Foreword

I am delighted to write this foreword to the Wellcome Science Review 2020.

I congratulate the entire Science Review team on the outstanding job they have done. Their painstaking and critical synthesis of thoughts and ideas, from beyond as well as within Wellcome, shines through.

This Science Review is profound for Wellcome, the world's second-largest medical research foundation, which has more than doubled its research expenditure in the last ten years. Indeed, the Science Review has crystallised a new and refreshed vision:

Wellcome supports science to solve the urgent health challenges facing everyone

This, in turn, defines and aligns Wellcome's scientific and organisational strategies to be accountable to, and to demonstrably achieve, that vision. In doing so, the full weight and expertise of Wellcome and its partners will be brought to bear – not only in the area of science, but also with respect to advocacy, policy, communication and public engagement.

Clearly the Science Review 2020 heralds a significant change for Wellcome, but it is an evolution rather than a revolution in the organisation's science strategy.

Firstly, recognising that most transformative discoveries arise from curiosity-driven research, Wellcome will continue to support, and in places diversify, its discovery research base. Traditional criteria of originality, excellence and rigour will be augmented by closer attention to research culture, diversity, inclusion, research environments and career structures. Disciplinary areas will be widened to tackle complex questions and scientific synergy will be encouraged throughout.

Secondly, recognising and responding to urgent and existential threats to human health, Wellcome will focus on three challenge areas: infectious diseases, mental health, and climate and health.

These challenge areas will include but will go beyond discovery research. For example, they will commission research through competitive calls and the coordination of teams to achieve specific goals. This might be with the aim of controlling, diagnosing and treating certain infectious diseases; of coordinating and translating mental health research into patient benefit; and of understanding and ameliorating the effects of global heating on human health. These huge but tractable challenges will be addressed with humility and in partnership with researchers and like-minded institutions worldwide. Inclusion of those most affected by these challenges, and their access to downstream solutions, will be core to these challenge-led programmes.

We believe these four things that Wellcome chooses to focus on will make the best use of Wellcome's independence – an independence that can ensure that:

- Discovery research is properly valued and supported, and that it maintains international perspective
- Infectious disease research, sharply illuminated by the COVID-19 pandemic, brings worldwide and accessible benefit
- Mental health, especially in the young, is properly addressed by combining and aligning relevant disciplines
- Climate and health has an institutional champion addressing this crucial aspect of global warming.

As a member of the Board of Governors, as a scientist, and as a citizen, I enthusiastically and deeply commend this Science Review and the forward mission and strategy it has evoked.

Sir Michael Ferguson
CBE FRS FRSE FMedSci FRSB
Deputy Chair
Wellcome Board of Governors

Executive summary

This review, launched in 2018, describes Wellcome's reassessment of how it funds science. It was carried out in response to the fact that since Wellcome's research funding started substantially increasing, in the 1980s, science has changed, the world has changed, and Wellcome has changed.

In carrying out the work we consulted broadly, speaking to people from within the Wellcome family and outside it, and seeking the views of individuals from many scientific and health-related walks of life, including research, funding, industry and policy. We spoke to people at many career stages, and in countries from around the world. We focused particularly on where Wellcome should be in 10–15 years and what major scientific and health challenges we should seek to overcome.

We also carried out an online survey of Wellcome's research community, receiving over 2,000 responses, and we performed our own analysis of the research funding landscape, to identify areas which already receive substantial funding and those in which Wellcome might take a leading role.

Finally, we reflected on the question of whom Wellcome, an independent charitable foundation that doesn't answer to politicians, taxpayers, shareholders, customers or donors, is accountable to. We concluded that we are accountable to society for delivering our charitable mission, and in doing so we are obliged to make best use of what makes us different from other funders. These distinctive characteristics include our independence, our perspective, and our relationships. Our new strategy would build on these foundations.

An early conclusion of our work was that in everything we do we should promote a healthy and productive research culture. Then, based on evidence from the review and from extensive discussion with Wellcome's Executive Leadership Team and Board of Governors, we concluded that Wellcome-funded science should enable science and innovation to tackle the greatest threats facing humanity, and that it should do so through a broad underpinning of discovery research together with research directed at specific health challenges.

In deciding that discovery research should remain a central part of our science funding we recognised that advances in health can come from unexpected sources, and a large number of health interventions have come from curiosity-driven fundamental research aimed solely at understanding how life works. By giving researchers the freedom to ask the most exciting and fundamental questions, we shall maintain a broad base of expertise and flexibility.

In deciding which health challenges Wellcome should focus on, we used three criteria: the urgency and scale of the threat; the opportunity for Wellcome to lead the way and make a difference; and the ability to harness what differentiates Wellcome from others. We decided that these criteria were best met by infectious disease, mental health, and the impact of climate change on health. In addressing these challenges we shall use the full weight and expertise of Wellcome and its partners — not only in science, but also in advocacy, policy, communication and public engagement.

Introduction

When we started this review of Wellcome-funded science at the end of 2018, Wellcome's mission was clear: it was to improve health for everyone by helping great ideas to thrive. But how best to do this? Wellcome had not carried out a fundamental review of how it funds research for many years – if ever – and it was high time we did so. In the more than 30 years since Wellcome started diversifying its investments, allowing it to grow into a major research funder, science has changed, Wellcome has changed, and the world has changed.

As a subject, of course, science is still a quest to understand how the world works. But the scope of research, particularly in biomedicine, has transformed over the last 30 years. We have sequenced the human genome, cloned mammals, and developed new techniques for modifying genomes; data science has transformed the way we work and think; team science and multidisciplinarity have come to the fore; and as a result, researchers are using new techniques to ask new questions every day.

Wellcome too has changed, especially with respect to its size and the amount it invests in science and research – from £28m a year in the 1980s to over £1bn in 2020. Over this period Wellcome has funded more people and more kinds of science than ever before, but there has been no real change in the way we work. We have not responded in a strategic manner to the ways in which science and health research have changed, and those changes that have been made have been incremental or have tended to add to what we do, leading to a portfolio of activities that may be too diverse to achieve significant impact.

In addition to this question of how Wellcome has changed is the matter of accountability. We need to know whom we answer to. I return to this later, but it's not simply a question of saying that 'Wellcome's job is to fund science', or that 'Wellcome is accountable to the people it funds'.

And finally, the world has changed. Those of my generation are aware that the antibiotics that were so freely prescribed when we were young are no longer the seeming cure-alls they were; we are also aware of the dangers of climate change, and how these will transform for ever the way we live; we know that mental illness is increasing, especially in young adults; and most recently the COVID-19 pandemic has demonstrated how fragile is human life in a changing world.

With these thoughts in mind we asked ourselves how Wellcome-funded science might best achieve Wellcome's mission of improving health. Our intention was that the review should:

- Establish a clear aspiration and bold ambitions for Wellcome-funded science
- Identify what changes Wellcome needs to make to achieve these ambitions, including structural and cultural changes as well as funding mechanisms
- Define realistic and appropriate ways to judge progress and success.

And in doing this work we applied three core principles:

- We asked where we wanted to be in 10–15 years, and worked backwards from there
- We agreed that nothing should be off the table; we wanted to be ambitious in our vision but realistic in our implementation
- We wanted our recommendations to be applicable for at least 10 years, and to be flexible enough to respond to changes in circumstances, whether scientific or budgetary.

How we approached the review

We recognised at the outset that a thorough review of Wellcome science would be a large undertaking, and one that should not be undertaken unadvisedly or lightly. We also recognised that carrying out such a review would inevitably lead to choices, and that choices are always tough. For these reasons we decided to take the necessary time, to consult widely, and to do the right research.

Thus, we spoke to people from many scientific and health-related walks of life, including those involved in research, funding, industry and policy, and at many career stages. We spoke first to people around the world who were outside our usual circles – to those we don't fund and those with whom we rarely partner. We thought it important to get new ideas and new perspectives early in our work, before our thinking had developed too far in any direction.

In consulting people, we used various means of communication, including in-person, video and phone interviews, university visits, international study trips, and surveys. We spoke formally at Wellcome researcher meetings and informally at panel meetings. We also used social media and other routes to invite comments from the research community.

We were open to any thoughts or comments – and a selection of these are published in this report. But we focused particularly on where Wellcome should be in 10-15 years and what major scientific and health challenges we should try to overcome. This involved asking questions about science and health research in general, about what are the big questions in biomedical research, about gaps in funding, about the benefits of partnership, and about different types of funding. We also asked about career structures, leadership, research culture, how to make decisions, what makes Wellcome different from other funders and what, therefore, our role should be. We are enormously grateful to everyone to whom we spoke – they are listed in the back of this review.

We did our own research too. We spoke to our colleagues in Wellcome; we drew on insights from our past performance, including data from the Wellcome Success Framework; and we looked at various other sources to get an impression of scientific priorities, funding gaps and scientific career paths. We also took the time to challenge ourselves on how best we might use our independence.

Each step of the review was discussed with Wellcome's Science Review Subgroup, our Executive Leadership Team and our Board of Governors.

Although we began our work with an intense phase of data gathering, it wasn't long before we were doing research and refining our strategy simultaneously. For simplicity, however, I describe our work linearly – in scientific writing parlance, I first present the Methods, then the Results, and then the Discussion. I do this to make our work and its logic easier to follow, although in presenting our work in this way I am reminded of Peter Medawar's famous question about whether the scientific paper is a fraud – not with respect to its contents, but with respect to the process of thought that gave rise to the work described. For this reason, I do insert here and there a comment about how the strategy actually developed in real time.

What did we learn?

This section summarises the lessons we learned from consultations outside the Wellcome community; from consultations within the Wellcome community; from a survey carried out with those we fund; from our own analysis of the funding landscape; and from our reflections about what Wellcome's role should be.

Consultations outside the Wellcome community

In our interviews and international study visits, we asked for ideas on what science and research funding might look like in 2035, along with what might be the biggest threats to human health. We discussed what the big scientific questions might be, how to support the scientists of the future, how to identify excellence, how to establish a good scientific culture, how to create the best conditions in which to carry out research, and how to promote good leadership.

Of the more than 250 people we spoke to, about half were early- or mid-career researchers. Their disciplines ranged from structural biology to behavioural research, plant sciences to astronomy. They came from academia (universities and independent research institutes), industry (pharmaceutical companies, biotech and tech), government funders and philanthropic funders, and they were based in the UK, Canada, Australia, Switzerland, Germany, France, Kenya, Uganda, The Gambia, China, Japan, Singapore and the USA.

Below are examples of the views we gathered. A larger selection of comments can be found in Annex 1.

Senior Vice-President at a biotechnology company in the US:

"The scientific enterprise won't look the same in 2035 as it does now, and it is important to support future generations of scientists as they will be the major drivers of change"

Professor of Developmental Biology at EPFL:

"Curiosity-driven research may no longer be as relevant if the world continues to get warmer and people are at risk of dying from infections after routine operations"

Former President at a university in the USA:

"Curiosity-driven research is the bedrock of all science, but funders have a responsibility to guide scientists to focus on the biggest challenges facing society"

Chair of a biomedical research charity in the UK:

"Wellcome is at its best when it is acting differently and backing bold ideas that others might not have supported"

The many stimulating and insightful views we heard led us to define four distinct options for Wellcome's science vision – high-level statements of what we seek to achieve. The four options were these:

1. Catapulting forwards the scientific fields of tomorrow. This would involve identifying and accelerating nascent scientific fields that have the potential to change significantly the science of human health.
2. Creating a new culture for better science. The objective here would be to create a healthy and productive research community and research environment.
3. Expanding the frontiers of science. There were two options under this heading. The first was to take the long view in creating knowledge by focusing on discovery-driven science. The second was to seize opportunities to produce new health interventions in the short term.
4. Bringing new ideas to humanity's greatest challenges. Here the idea was to focus science and innovation on tackling the biggest health challenges facing humanity.

Over the course of the review we tested these options with a wide range of people and in the context of our own data analyses, to help us refine our thinking and select our preferred vision.

The Wellcome community — internal discussions, university visits and researcher meetings

After speaking to people outside our usual circles we turned to members of the Wellcome community—those who work with us and those we fund. Internally, we first carried out a formal survey of Wellcome's Science Division and then arranged a more informal workshop with the Division. These were followed by café-style workshops involving all Wellcome colleagues, and question-and-answer sessions with members of the Science, Grants, Policy, Innovations, Culture and Society, Insight & Analysis and Diversity & Inclusion teams, as well as with each of the Wellcome's Priority Areas. Throughout the review we spoke to members of Wellcome's Executive Leadership Team and members of the Board of Governors. We are enormously grateful to all our colleagues for their insightful comments.

Externally, we gathered views during town hall meetings at the Universities of Leeds and Cambridge, during researcher meetings, and in written correspondence. The comments we received were also extraordinarily valuable in helping develop and refine our ideas; a selection of these can be found in Annex 2.

A quantitative survey

In August 2019 we launched an online survey for the research community, to gather opinions on ideas relating to our preliminary visions. We focused on our first, third and fourth options, because by this time we had agreed that creating a healthy and productive research culture would be part of whatever we decided to do; we explored research culture in a separate survey carried out as part of Wellcome's Research Culture campaign. The survey was sent to Wellcome grant-holders, to unsuccessful applicants from the past five years, to committee members, and to those we had already consulted during the review. We received 2,160 responses in the four weeks the survey was open.

We note that the survey data do not accurately represent the research community at large. The average respondent was older than the average of those we contacted, with 78% of respondents being senior researchers. Fewest responses (6%) were from those aged 20-29. Researchers spanned the basic-to-translational spectrum, with about 36% on the basic end, 35% translational or involved in implementation, and the rest in between. Responses were mostly from academia (84% universities and 8% independent research institutes), but we also received responses from industry, charities, government funders and the NHS, as well as some artists, publishers and museums. We obtained only limited demographic data, but of those who gave us this information 55% were British, the same percentage were male, and 87% were white. Unsuccessful applicants had similar backgrounds to those who had been successful.

Key findings from the survey as they relate to the vision options are in Annex 3.

Wellcome's analysis of the funding landscape

It was important to understand the areas in which Wellcome and other funders have supported science over the last decade or so, so that we could identify any areas which appear to receive particularly generous funding, and any areas in which Wellcome might now take a leading role.

For comparators, we focused on the funders used by Wellcome's Insight and Analysis team in their work on Wellcome's Success Framework. These comprised a mix of governmental and philanthropic funders from the UK and globally. They included the Biotechnology and Biological Sciences Research Council (UK), the European Research Council, the National Natural Science Foundation of China, the British Heart Foundation, the National Institutes of Health (USA), the Medical Research Council (UK), the Bill and Melinda Gates Foundation (USA), and the National Institute for Health Research (UK). Each spends at least $100m per year on research, and each has a focus on biomedical science or human health, making them reasonable comparators for Wellcome.

In defining basic and translational science, we used categories defined by Wellcome's Insight and Analysis team based on the UK Health Research Classification System. At the basic end these include underpinning research and aetiology, and go on to cover prevention, detection and diagnosis, treatment development, treatment evaluation, disease management, and health services in translational science.

The key results of this analysis are presented in Annex 4.

Citation analysis – a measure of how influential the research is – revealed that for all funders, translational publications are referred to slightly more frequently than basic publications. Nevertheless, most funders, including Wellcome, spend more on the basic end of the research spectrum. Of the comparators we chose, the only exceptions were the Bill and Melinda Gates Foundation and the National Institute for Health Research, who both fund more translational research than discovery.

In the course of our consultations we had heard frequently that the major health challenges facing humanity include climate change, antimicrobial resistance and mental health. We found, however, that relatively little was being invested in dealing with these health challenges, especially in antimicrobial resistance and climate and health, so we viewed these as potential opportunities for Wellcome (see Annex 4). We also recognised that if we were to support discovery research, there might be an opportunity to do it differently from other funders.

Reflections on accountability and what makes Wellcome different

The final question we discussed, that of whom Wellcome is accountable to, is a profound one. As an independent charitable foundation we receive tax breaks and we have significant influence in biomedical science and beyond. But we don't answer to politicians, taxpayers or shareholders, nor to customers or donors. Wellcome may think it does good things, but in the absence of anyone to hold us to account, who are we to say?

We have reflected on this question over the last 18 months. We have concluded that Wellcome is accountable to society for delivering its charitable mission, and in doing so is obliged to make best use of what makes us different from other funders. This latter point is directly relevant to the design of our strategy, and we have concluded that there are three areas that collectively distinguish us from others. These are our independence, our perspective, and our relationships.

Independence

As a foundation, we have the freedom to set the goals and timeframes we choose and to take on challenges that others find difficult or impossible

Perspective

Wellcome has a distinctive perspective on health and how to improve it – we understand how to get the best out of science by integrating it across the whole of society, including, but not limited to, innovation and cultural engagement

Relationships

At the scale we are today, Wellcome is able to give researchers the space to explore, to set shared goals with our partners and the people we support, and to bring people together to make a difference to the health of all humankind

These distinctive qualities informed directly the development of our new strategy.

Wellcome's science strategy: where we got to

The first iteration of Wellcome's new strategy was based on our conversations with the community external to Wellcome, which resulted in the four visions outlined above. This initial work was presented to Wellcome's Board of Governors in June 2019. It was clear from that meeting that it would not be possible to pursue all four visions, but that it might be possible to combine two in a portfolio approach. In particular, we agreed that research culture (encapsulated in the second option) was important enough that it should be embedded in everything we do, and this informed all our subsequent conversations.

We did a lot of work between June and our next meeting with Wellcome's Board of Governors in November 2019. We spoke to the Wellcome community, carried out our quantitative survey, analysed the funding landscape, and assessed what makes Wellcome different. As a result, in the course of the November meeting, we made the decision that Wellcome-funded science should enable science and innovation to tackle the greatest threats facing humankind, and that it should do so through challenge-led research (in essence, the fourth option described above) and through a broad underpinning of fundamental science that creates new knowledge and new training opportunities (the first part of the third option).

Wellcome-funded science should tackle the greatest threats facing humankind, through challenge-led research and a broad underpinning of fundamental science

These were significant decisions. They reinforced the primacy of discovery research in Wellcome's portfolio, and by taking on challenge-led research that addresses the greatest threats facing humankind they allow Wellcome to focus its efforts much more clearly than hitherto. The next task was to decide on the health challenges we should focus on.

The health challenges

We devoted much time to thinking about how many health challenges Wellcome might address and what they should be. In thinking about this we applied an over-arching criterion that the challenge should be tractable and that research should be able to contribute to the solution to the problem. We also considered the following questions:

1. **The urgency and scale of the threat.** Is the challenge to human health and wellbeing universal? Will it be felt more acutely in resource-poor settings? Will it result in premature disability or death and be felt more keenly by future generations? Is the trajectory of the challenge increasing, with a pressing need for action? Is it an issue that we cannot currently manage or control? Are concerns growing across society?
2. **The opportunity for Wellcome to lead the way and make a difference.** Is the challenge underfunded by public and private research spend in high-income countries? If Wellcome acts, is it possible to reduce health inequalities in this area? Are the required approaches ones in which Wellcome is, or might become, credible and competent?
3. **The ability to harness what differentiates Wellcome from others.** Would solving the challenge make the most of Wellcome's independence? Would it benefit from Wellcome's distinctive perspective on health and how to improve it? Would it benefit from Wellcome's scale and relationships?

At a Governors' meeting in February 2020 we applied these three criteria to eight potential health challenges: infectious disease; mental health problems; the impact of climate change on health; multimorbidity; nutrition and metabolic diseases; cardiovascular diseases; cancers; and neurodegenerative conditions. We decided that our criteria were best met by the first three of these challenges: each carries the risk of significant premature disability and death in future generations and each will be felt most keenly by minoritised or resource-poor populations. For each, we could make the most of Wellcome's strengths to support a continuum of work from discovery research to translation and implementation, and this would be complemented by work in advocacy, policy, public engagement, communications and education.

Infectious disease

Our assessment of infectious disease as a health challenge was particularly influenced by the high disease burden among the poorest communities in low- and middle-income countries, where most outbreaks occur and where the risk of future epidemics is highest[1]. Even while we were doing this work, during 2019, the World Health Organization commented that larger outbreaks are becoming ever more frequent and more complex (this was exemplified by the continuing Ebola, cholera, typhoid, Zika and 2019-nCoV outbreaks during that year)[2,3]. In the last ten years, the average time for microbes to develop resistance to a previously effective drug has halved and the incidence of antibiotic resistance is increasing[4]. Modelling (carried out before the COVID-19 outbreak) predicted that a flu pandemic could kill ~33 million people within six months[5].

In considering infectious disease as a potential health challenge for Wellcome we recognised that other funders are active in this field, but that some areas are not being addressed – these include neglected tropical diseases and escalating diseases, as well as improving racial, ethnic and gender diversity in clinical trials[6,7]. We also noted that existing work is fragmented and not making use of common or shared methods and approaches which could accelerate progress.

Infectious diseases also meet our last criterion about harnessing what makes Wellcome different, especially because there is a need for work that traverses science and other areas including policy, social sciences and public engagement. Wellcome is respected on the international stage, which, combined with our independence, gives us a compelling voice and the ability to convene others.

Mental health

Mental health problems have been recognised by several organisations, including the World Health Organization, as one of the major health challenges facing humanity, and they are expected to be the main cause of global morbidity by 2030[8]. Despite the scale of the problem, fewer than 20% of people with common disorders such as depression and anxiety receive appropriate treatment in high-income countries, and the figure is significantly lower in low- and middle-income countries[9]. With relatively little scientific progress in the last 30 years and very few new therapies or therapeutics, this represents a clear opportunity for Wellcome, not least because large pharmaceuticals have pulled out of mental health research (mental health is not a priority for six of the seven pharmaceutical companies with revenues over US$30bn).

By entering this area Wellcome can make use of what makes us different, including our perspective on research into mental health interventions and neuroscience, our strong portfolio of basic research, and our new Priority Area in Mental Health, which has focused on anxiety and depression in young people. Wellcome could address the problem in many different ways across science, as well as in other areas including policy, social science and public engagement. We also have a growing reputation on the international stage in this area, having partnered with the WHO and with the UN and having led sessions at the World Economic Forum in 2019 and 2020. There is also an opportunity for Wellcome to lead efforts to reshape the field in order to develop more effective interventions.

Climate and health

Climate change has been noted by many organisations, many researchers and many individuals as the single biggest challenge facing human health[10,11,12]. The scale of the problem is increasing rapidly, with the largest impact felt in low- and middle-income countries: between 2030 and 2050, climate change is expected to cause about 250,000 additional deaths per year[13].

Although the challenges of climate change are widely recognised, there is not enough tangible action, especially with respect to the health impacts of climate change. This may be because climate is not traditionally recognised as a health issue, especially since organisations such as the Rockefeller Foundation have moved away from climate. Furthermore, only one of the seven pharmaceutical companies with revenues over US$30bn carries out research in an area related to climate (Bayer on crop science). There is thus plenty of opportunity for Wellcome to lead the way and make a difference.

And with respect to our final criterion, the impact of climate on health harnesses those qualities that make Wellcome different, both because it is an issue that benefits from our independence and ability to take a long-term view, and because it requires a multidisciplinary partnership-based approach. Although Wellcome's reputation in the area is limited, the approaches required to make climate a health issue and to ensure research has an impact are ones in which Wellcome could become credible and competent.

These three health challenges – infectious disease, mental health, and climate and health – are important in themselves, but it's also important to note how they interact with each other, and how much value there will be in exploring all three under one roof. For example, climate change will affect the distribution and burden of vector-borne disease, and we know from the COVID-19 pandemic how infectious disease outbreaks can affect mental health. We shall be alive to any such opportunities in the future.

Discovery research

Turning to discovery research, all the conversations we had, and all the research we did, made it clear that advances in health will come from unexpected sources, and indeed that a large number of health interventions have come from curiosity-driven fundamental research aimed solely at understanding how life works. As other funders invest less into discovery research (perhaps inevitable in the face of the COVID-19 pandemic) it becomes more important than ever for Wellcome to contribute to knowledge and understanding, and thereby to solve not only our own health challenges, but also challenges in other areas of health and wellbeing. By providing the best scientists in clinical and non-clinical research, and in the humanities and social sciences, with the freedom to ask the most exciting questions, Wellcome will play to its strengths and provide the seed corn that is necessary for progress in science and health and the economy.

Research culture

The second of our four preliminary visions was of promoting an environment and culture in which research can flourish. This vision was subsumed into the strategy as a whole, but this was not to belittle its significance – on the contrary, improving research culture will be embedded in everything we do. This speaks to diversity and inclusion, and our desire that science as a career is open to everyone; that experiments are designed with diversity and inclusion in mind; and that everyone benefits from Wellcome-funded research. It also speaks to leadership, to open science, and to research integrity. You'll be hearing much more about this elsewhere.

Reflections

I am pleased with the way the strategy has turned out. In particular I am delighted that Wellcome will continue to support discovery research – we simply don't know where the best ideas will come from, or how they might contribute to advances in health, and the only route to success is to support a broad range of bold research carried out by the most innovative people.

I'm also pleased that we'll use the weight of Wellcome to address our three health challenges of infectious disease, mental health, and the effect of climate change on health. I write in August 2020, amid COVID-19, increasing concerns about mental health, and a heatwave. I cannot claim that we were particularly prescient in choosing these three areas, but I am struck by the ways in which they overlap and the potential that is offered by housing the three areas in Wellcome.

We are still working on some elements of the strategy. For example, we are asking how we will fund discovery research, how we will assess applications, how we will support careers and encourage multidisciplinary applications, and how we will support the directed elements of Wellcome's discovery. We are also discussing how best we can support our three health challenges – where we will focus our work, how Wellcome might provide strategic as well as scientific support, and with whom we can partner. You'll hear about these areas, and more, later.

Jim Smith

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- Japan Science and Technology Agency
- Makerere University
- Max Delbrück Center for Molecular Medicine (Helmholtz Association)
- Max Planck Institute of Molecular Genetics
- MRC/UVRI & LSHTM Research Unit
- National Institute of Biological Sciences (Beijing)
- National Natural Science Foundation of China
- Okinawa Institute of Science and Technology
- Peking University
- Relay Therapeutics
- RIKEN
- Robert Koch Institute
- Rockefeller Foundation
- Shonan iPark
- Sloan Foundation
- Sony Computer Science Laboratories
- Tsinghua University
- University of Cambridge
- University of Leeds

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Annex 1

A selection of comments made to us during our consultation with the external community.

President at a charitable foundation in the US:

"You have to recognise that an important part of science is the scientist"

Professor of Radiology at Harvard Medical School:

"Data scientists will be key team members in the future enabling us to deliver reproducible and robust science"

President at a research institute in the USA:

"In order to achieve real impact on science and health, you have to think and act globally"

Historian at the University of Oxford:

"Wellcome does need to be 'known' for something and be able to demonstrate its impact on the world"

Senior leader at the World Health Organization:

"Discovery research is inherently unpredictable and you never know what discoveries might prove to be game-changing"

Researcher at the University of Oxford:

"New tools and technologies are enabling science to begin to explore the deepest areas of the unknown"

Executive Director at RIKEN:

"Recent advances in science and technology have the potential to transform existing or create entirely new fields of research"

Founder of a medical research charity in the Gambia:

"Researchers of all backgrounds must be able to see a clear pathway of progression and feel empowered to become the leaders of the future"

Senior Scientist at the European Molecular Biology Laboratory:

"Postdoctoral researchers face a bottleneck during the transition to independence and the enterprise loses a lot of talent at this stage – there is simply not enough career stability"

Founder at a charitable foundation in the US:

"Grant writing may have its virtues, but it takes up a lot of researcher time that could be better spent on doing research"

Professor of Immunology at King's College London:

"The mark of good leadership is taking pleasure in the achievements of others"

Senior leader at the Agency for Science, Technology and Research (A*STAR):

"Wellcome is part of an international community of funders and cannot do everything on its own"

Annex 2

A selection of views expressed to us from members of the Wellcome community, including grant-holders and staff.

- It's good for organisations like Wellcome to take stock
- Wellcome is perceived to be at its best when it is being opportunistic and taking risks on people without a track record, giving them the flexibility and freedom to pursue their ideas
- Funders should develop success measures, but at the same time acknowledge that this can be challenging in the area of knowledge creation
- Wellcome's support of smaller labs is valuable because they foster creativity and can harness the power of big data
- There was enthusiasm for the idea that Wellcome should support research at all career stages, early and late, so that researchers should not think there is a time limit on their careers
- Many acknowledged that to tackle existential health threats Wellcome would need to fund research in countries where people are most affected by the challenges
- There was support for Wellcome funding more generously and for longer
- There was a feeling from some that mid-career researchers had been abandoned in favour of focusing on schemes for early-career and well-established researchers
- Many emphasised the need to recognise the success of teams rather than putting certain individuals on a pedestal
- A new funding strategy should seek to develop further the human element of the relationship between research funders and researchers
- Wellcome sometimes places too much emphasis on funding senior investigators at the expense of more junior scientists
- Knowledge creation is seen as distinctive to Wellcome and is what Wellcome science is known for among much of the community.

Annex 3

The following data summarise selected key findings from an online survey consultation we conducted with the research community to gather opinions on ideas relating to three of our preliminary vision options and to ask where we might focus within each of the visions. Questions related to our second vision were explored in a separate survey as part of Wellcome's Research Culture campaign.

The survey was sent to Wellcome grantholders, to unsuccessful applicants from the past five years, to committee members and to those we had already consulted during the review. We received 2,161 responses in the four weeks the survey was open.

Analysis showed that the survey data do not represent the research community at large:

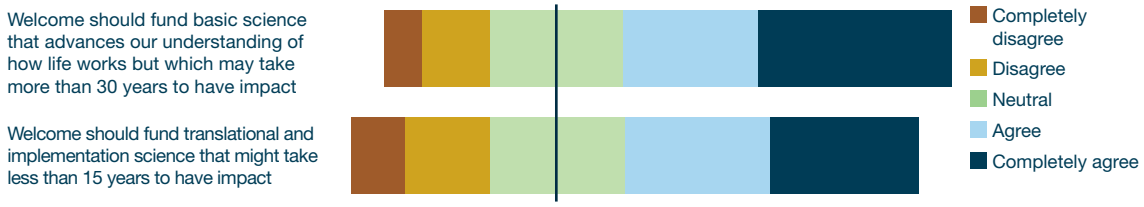
- Responses were mostly from universities (83.5%) and independent research institutes (7.6%), but we also received responses from industry, charities, government funders and the NHS, as well as some artists, publishers and museums
- The average survey respondent was older than the average of those invited to participate, with 78% of respondents being senior researchers
- The lowest response rate was from those aged 20-29 (~6%)
- Non-Wellcome-funded respondents had similar demographic backgrounds to Wellcome-funded respondents
- Researchers spanned the basic-to-translational spectrum, with about 36% on the basic end, 35% translational or involved in implementation, and the rest in between
- We obtained only limited data on diversity and inclusion, but 55% of respondents who gave diversity data were British, the same percentage were male, and 87% were of white ethnicity.

Throughout the survey, we used the terms basic, translational and implementation science which were defined according to the Health Research Classification System. We assigned the following research activity codes to each term: Basic= 1-2, Translational= 3-6, Implementation= 7-8.

Figure 1:
Should Wellcome focus on 'Catapulting forwards the scientific fields of tomorrow'?

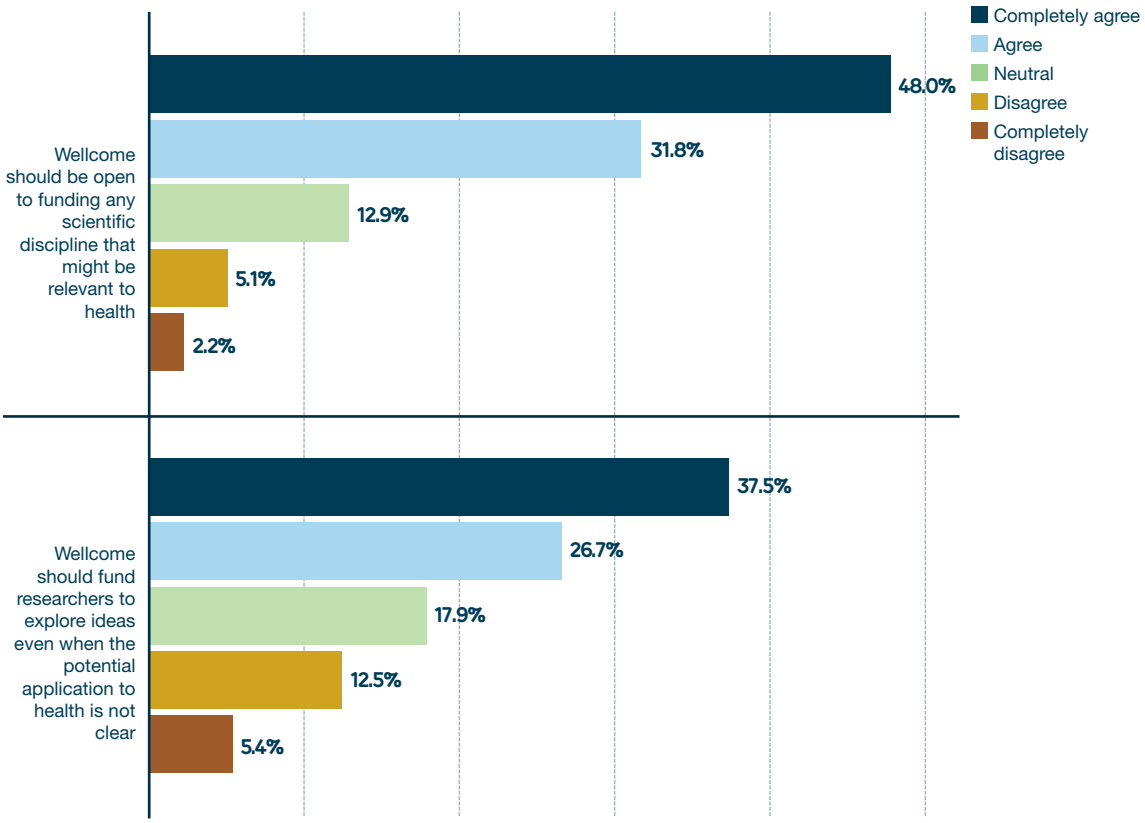
Respondents were most commonly neutral about Wellcome supporting new or underdeveloped scientific fields.

Figure 2:
Views on the timescales for 'Expanding the frontiers of science'



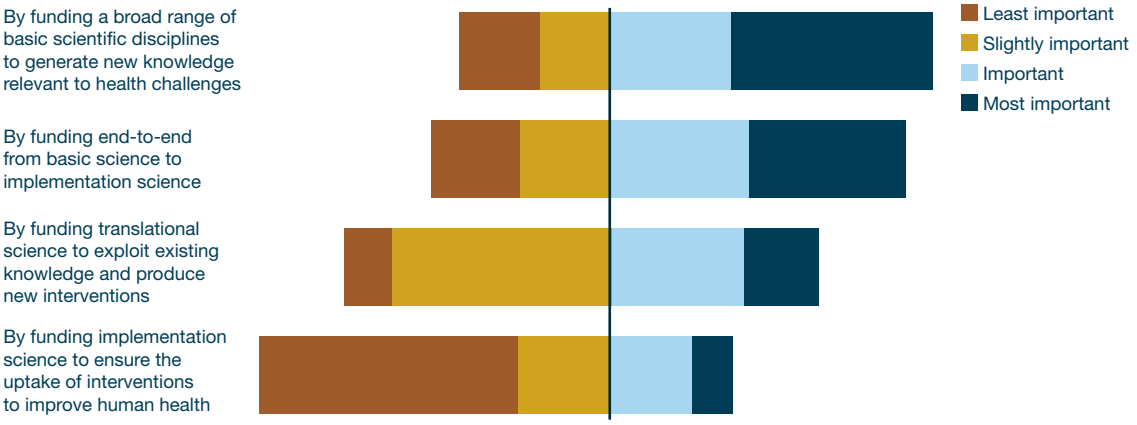
Survey data showing respondents' views on Wellcome's role in funding on research which may take 15 or 30 years to have impact. Most respondents agreed that Wellcome should support research with both medium- and long-term impact.

Figure 3:
The breadth of disciplines and research activities that Wellcome should support when 'Expanding the frontiers of science'



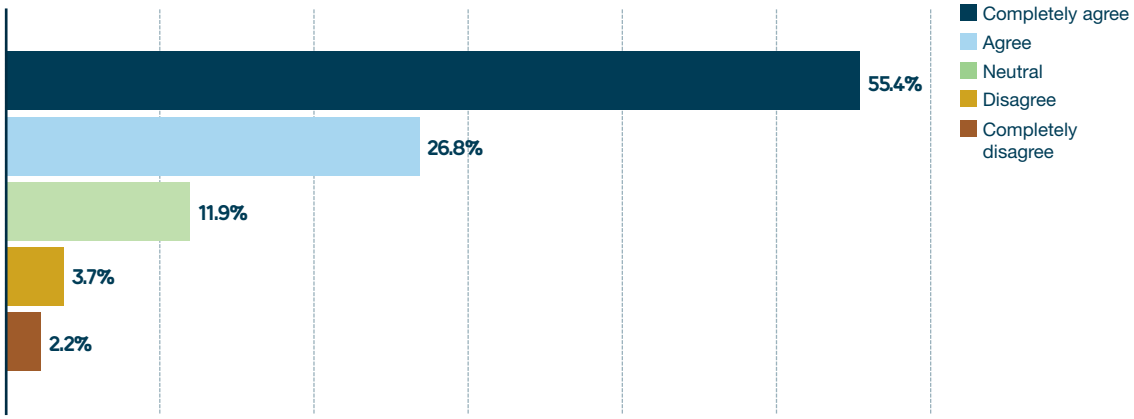
Survey data showing respondents' views on the breadth of disciplines and research activities that Wellcome should support. Most respondents agreed that Wellcome should be as broad as possible in the research we support.

Figure 4:
How Wellcome can best approach being 'The scientific engine bringing new ideas to humanity's greatest challenges'



Reponses to the question: "How can Wellcome best address the greatest health challenges facing human beings? Please rank the following options in order of importance from most important (1) to least important (4)". Respondents most often ranked 'by funding a broad range of basic scientific disciplines to generate new knowledge relevant to health challenges' as most important.

Figure 5:
Whether interdisciplinary research is needed for 'bringing new ideas to humanity's greatest challenges'



Survey data showing respondents' views on the role of interdisciplinary research in addressing major health challenges. Most respondents agreed that supporting interdisciplinary research is necessary to tackle major health challenges.

Annex 4

The following data summarise where Wellcome and other major health research funders have provided money and seen resulting publications from 2012-2016 inclusive. This analysis helped us understand where different vision options would place Wellcome within the wider funding enterprise and whether a particular vision would complement or overlap with other funding activities.

For comparators we focused on the funders used by Wellcome's Insight and Analysis team in their work on our Success Framework. We compared Wellcome with the Biotechnology and Biological Sciences Research Council (BBSRC), the Bill and Melinda Gates Foundation (BMGF), the British Heart Foundation (BHF), the European Research Council (ERC), the Medical Research Council (MRC), the National Institutes of Health (NIH), the National Institute for Health Research (NIHR) and the Natural Science Foundation of China (NSFC). All comparators spend a minimum of $100M per year and have a focus on biomedical science and/or human health.

We used publication and funding data provided by Uber Research Dimensions to conduct the analysis. Limitations of the data and analysis include:

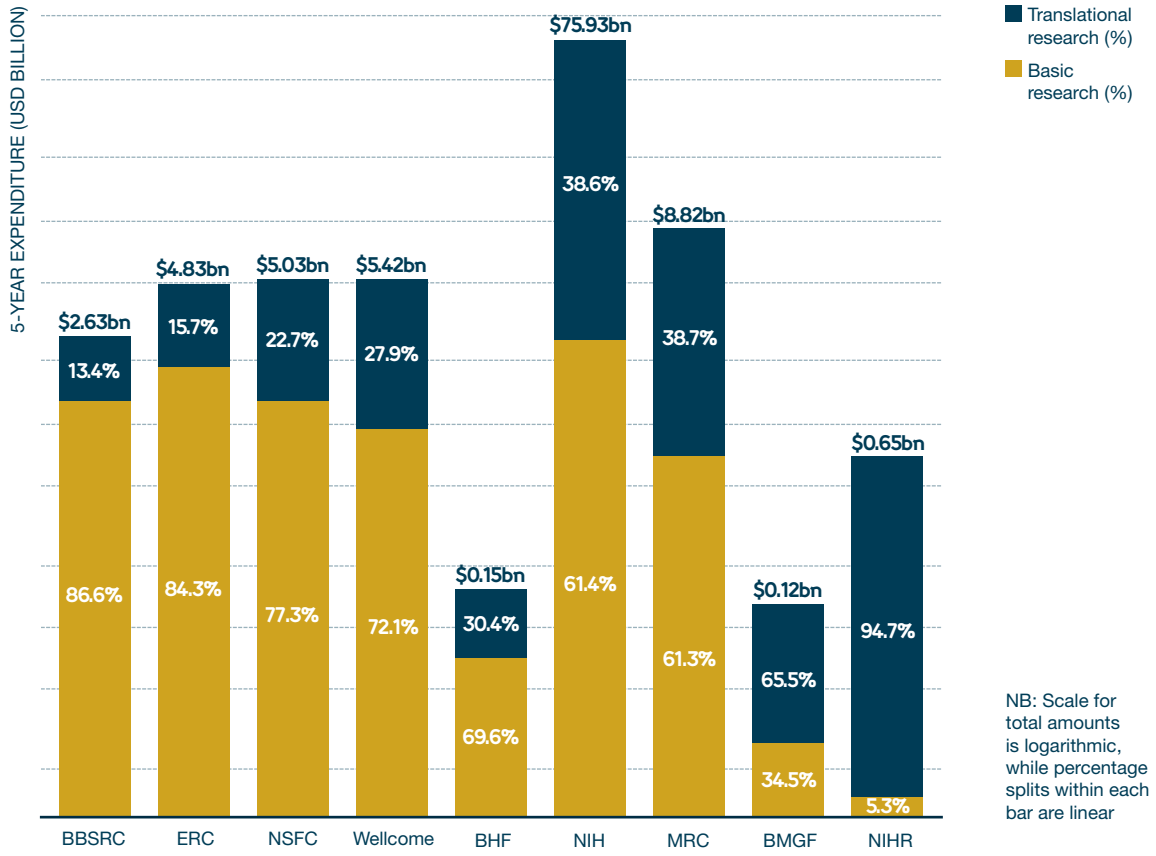
- The analysis was conducted in summer 2019 and the most recent year for which complete data were available on Uber Dimensions was 2016. This matched the time period that the Wellcome Success Framework analysed
- Grant funding data are sparse and not fully reported for all funders (i.e. the exact amounts of funding cannot be assumed to be accurate), limiting the direct comparability of funders although the funding trends and patterns remain useful
- Publications and grants are tagged automatically and not all data will be tagged according to specific subject matter or stage of the research pipeline. Incorrect and missing tags were assumed to be missing at random.

Due to the above limitations, we did not conduct statistical analyses on the data, presenting only general trends and patterns. Similarly, because the data provide only an indication of overall funding and publications trends, it is not possible to compare specific funders directly.

Notes on the presented findings:

- When analysing the data, we looked at temporal trends and found no notable differences in any of the proportions across the five years; therefore, we present the aggregated results across 2012-2016
- For defining basic and translational science, we used categories defined by the Health Research Classification System. To simplify the analysis and align with the Wellcome Success Framework report we dichotomised the data, classifying 'underpinning research' and 'aetiology' as basic science, and 'prevention', 'detection and diagnosis', 'treatment development', 'treatment evaluation', 'disease management', and 'health services' as translational science
- We heard repeatedly in our consultations that the major challenges facing humanity are climate and health, antimicrobial resistance and mental health. We therefore used these as the major health challenges in the analysis
- Subject matter tags are only applied to grants and publications that explicitly mention mental health, antimicrobial resistance or climate change; there may be basic publications and research grants that underpin these areas that have not been captured.

Figure 6:
Proportion of funding spent on basic versus translational research over a 5-year period (2012-2016) by major health research funders



Uber Dimensions funding data showing the proportion of funding spent on basic versus translational research over a 5-year period (2012-2016) by major health research funders. Most funders spent more on basic research than translational research.

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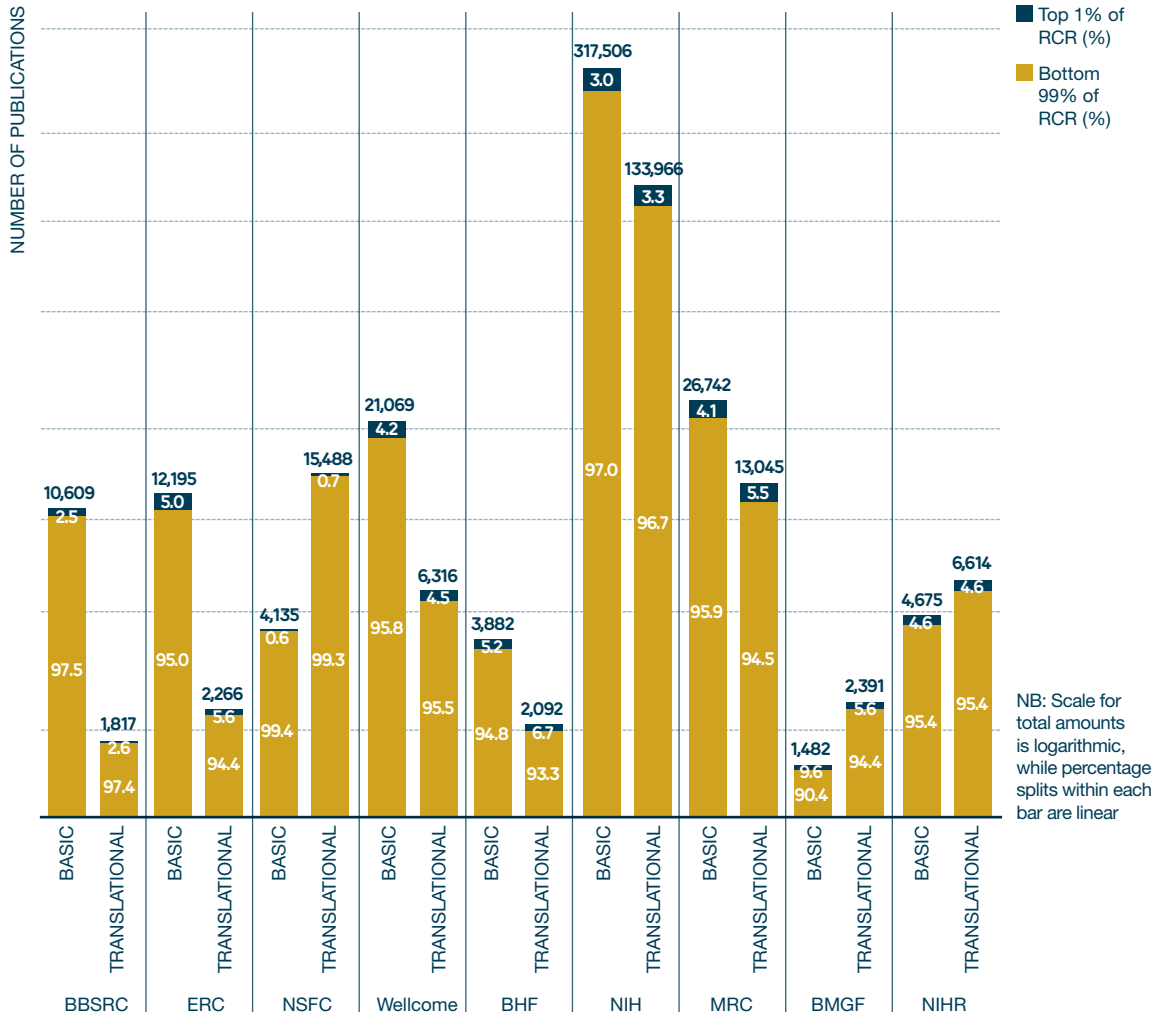
Figure 7:
Proportion of publications that were in the top 1% of RCR for basic versus translational publications by research funder



Uber Dimensions publication data showing the proportion of publications that were in the top 1% of RCR for basic versus translational publications by research funder. For most funders, there is a trend towards translational papers being slightly more highly cited (a proxy for impact) than basic research publications.

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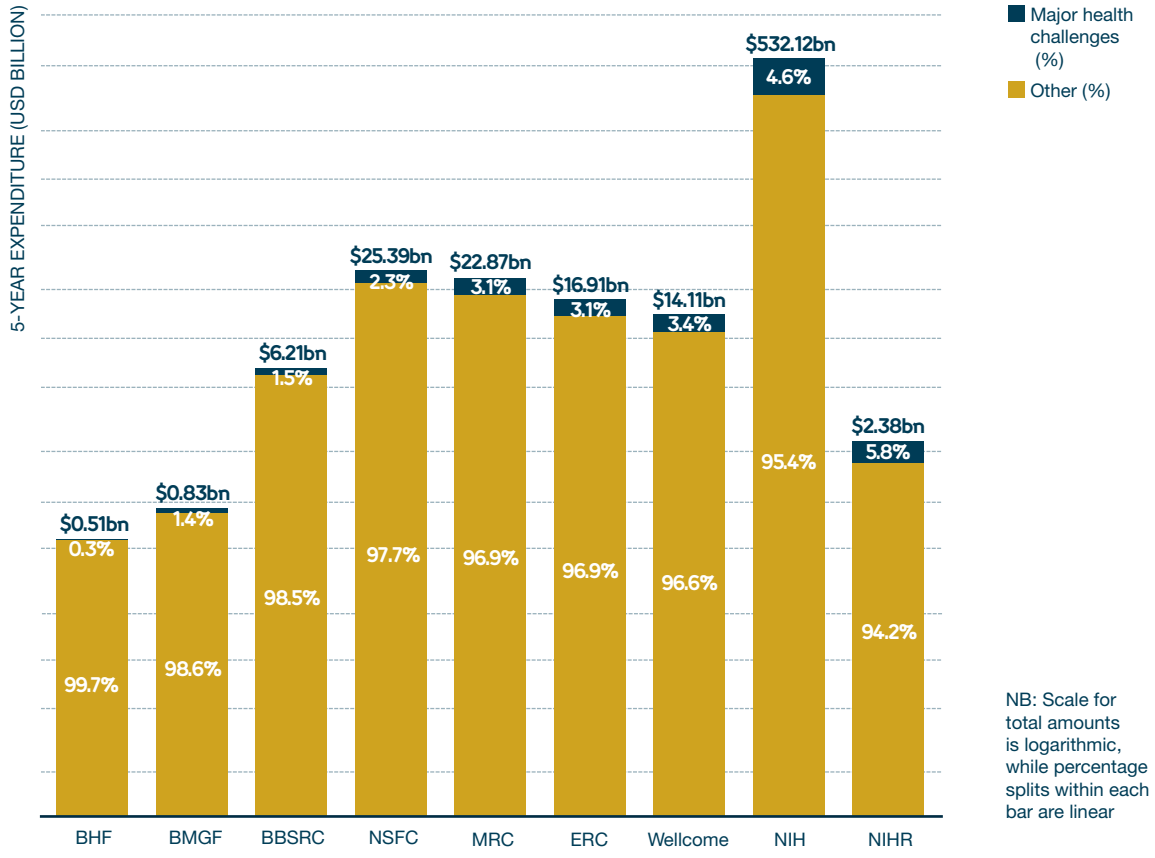
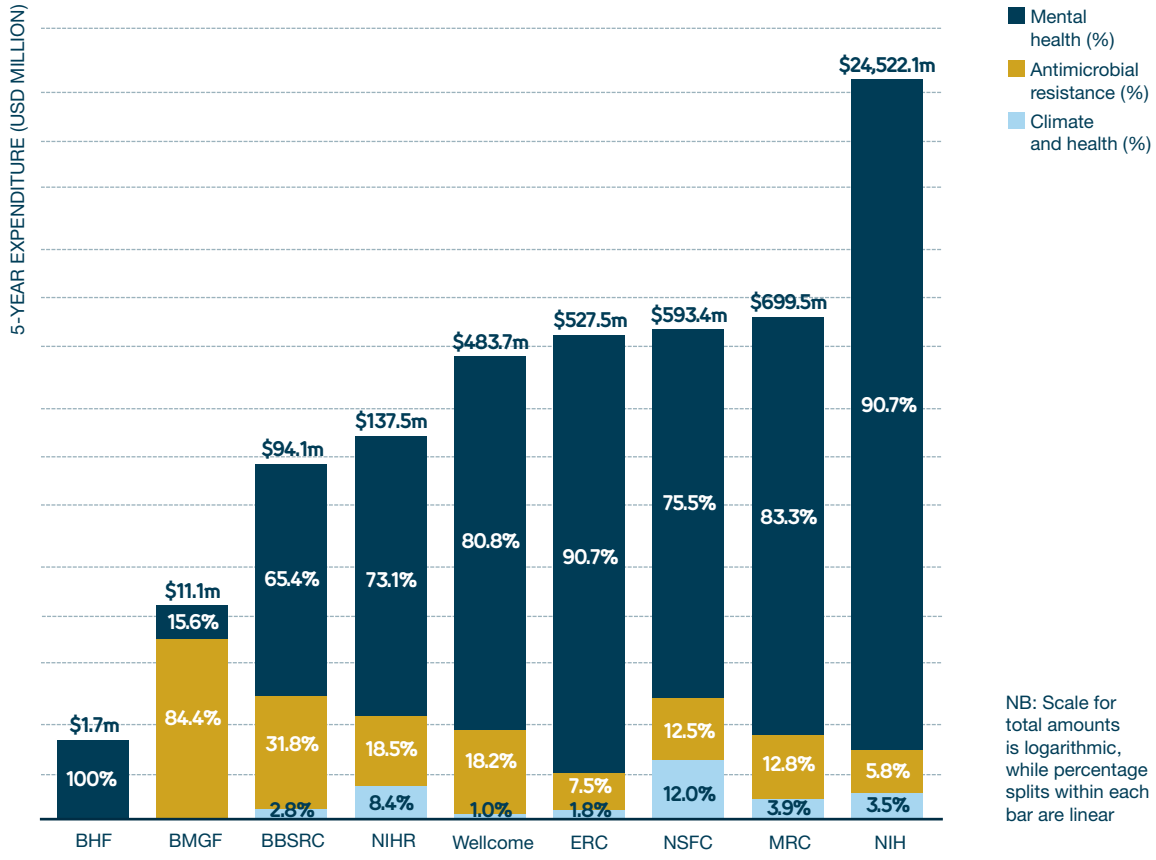
Figure 8:
Proportion of funding spent on major health challenges (climate and health, mental health, and antimicrobial resistance as a proxy for infectious disease) compared with other research activities over a 5-year period (2012-2016).



Uber Dimensions funding data showing the proportion of funding spent on major health challenges (climate and health, mental health and antimicrobial resistance as a proxy for infection) compared with other research activities over a 5-year period (2012-2016). Funders spent a smaller proportion on major health challenges during this period compared with other research activities.

Figure 9:
Overall expenditure on health challenges, the proportion that was spent on each over a 5-year period (2012-2016).



Analysis of Uber Dimensions funding data showing, of the overall expenditure on health challenges, the proportion that was spent on each over a 5-year period (2012-2016). For most funders, the highest proportion of spend on the health challenges went to mental health.

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