

# anualreview PHG FOUNDATION

022

making science work for health

### Director's message

2022 has been an excellent year for the PHG Foundation, not least because we have finally returned to business as usual at our offices in Cambridge, UK - whilst retaining the many benefits of digital connectivity. The team has produced some outstanding policy research and analysis, set out in our reports, briefings and other publications, and we have been pleased to undertake several fascinating pieces of commissioned work for national and international partners.

Towards the end of the year, we achieved a major milestone as we began our 25th year of operations since we were founded in 1997 as the Public Health Genetics Unit. A new book based on independent research into the history of genetics and genomics policy in the UK reveals what a very long way policy, health and genetics have come in this time - as has the PHG Foundation.

We look forward to celebrating this important anniversary with some major events for our stakeholders in early 2023, but this year has also been significant for me, marking ten years at PHG and five as Director.

In this time, I have been pleased to see our expertise, impact and reputation grow alongside our unceasing efforts to making science work for health. This mission remains as vital today as it was twenty-five years ago. Whilst genomic and related technologies and their medical applications have grown and continue to evolve, healthcare needs and challenges are also increasing.

As I prepare to hand over the leadership of our talented team to a new Director in the coming year, I am confident that PHG is well placed to identify and address the policy challenges of the years ahead and help ensure science and technology are used to the very best effect for health.

Mark Kolog

Dr Mark Kroese Director



## International partnerships

Making science work for health is very much a global endeavour, and we are internationally recognised for our expertise and policy insights in genomics, data and personalised medicine. We are always delighted to work with international partners on projects of mutual interest.

Over the last year we have been part of two major research consortia. The European network staff eXchange for integrAting precision health in the health Care sysTems (ExACT) project seeks to build and strengthen a community of multidisciplinary researchers. Two PHG staff visited partner organisations as part of this programme. Dr Sowmiya Moorthie, Senior Policy Analyst (Epidemiology) spent time at the European Public Health Association, based in Utrecht, whilst Tanya Brigden, Senior Policy Analyst (Biomedical Ethics) went to the Council of Canadian Academies in Ottawa.

PHG is also part of the new Personalized Prevention roadmap for the future of HEalThcare (PROPHET) project, a four-year multidisciplinary, pan-European initiative examining innovative technologies for personalised prevention of chronic diseases. As part of this programme, we are examining the scientific and clinical evidence for the use of biomarkers and digital technologies, working alongside colleagues at the Instituto de Salud Carlos III in Madrid.

Further afield, we continue our partnerships in Hong Kong, most notably with the Centre for Medical Ethics and Law (CMEL) at the University of Hong Kong led by Dr Calvin Ho, but also engaging with the Hong Kong Academy of Medicine (HKAM) on genomic medicine and AI in healthcare.

Finally, we have been pleased to continue working with international organisations including the Foundation for Innovative Diagnostics and Health Action International on projects relating to the use of technologies for the control of infectious diseases.











## Scientific horizons

Our rolling programme of horizon-scanning for innovative science and technologies and their potential applications for health provides invaluable intelligence for the PHG Foundation. We also publish policy briefings on selected topics, and undertake commissioned work to inform external partners. Some of the subjects we examined in 2022 included:

#### Near patient pathogen sequencing

In a new report for FIND, the global alliance for diagnostics, we built on previous work exploring the use of genome sequencing technologies for the detection and control of infectious disease agents, to examine the emerging landscape of sequencing tools for use away from large, centralised laboratories. This approach can offer quicker, more flexible and responsive sequencing services. We set out how such approaches are being used in lower, middle and high income countries, and provided a gap analysis of the requirements to support use in lower resource settings.

#### **CAR-T cell therapies**

Immunotherapy is a new form of treatment that harnesses normal immune system responses to target cancer cells. CAR-T therapies use genetically modified white blood cells and have shown success in patients as a treatment of last resort. However, our analysis revealed that further research is needed to address issues including dangerous treatment sideeffects and expensive and complex manufacturing processes.

#### Xenotransplantation

Another potential medical application of genetic engineering advances is for the modification of animal organs for human transplantation. Our research concluded that xenotransplants (between species) could offer a solution to current shortages of human donor organs, but technical, ethical, legal and regulatory barriers remain.

#### Precision medicine for inflammatory bowel disease

Inflammatory bowel disease (IBD) is a serious and debilitating chronic condition. Whilst a range of treatments exist, control of the disease is often poor and can require surgical interventions. Both pharmacogenomic and predictive genomic testing could offer improved insight into the best therapeutic approaches for each patient; however, more research evidence is needed to demonstrate clear clinical benefits.

#### Long-read sequencing

One of the innovative techniques in genomics that received increased attention in 2022 was long-read sequencing (LRS), an approach that decodes larger segments (over 10,000 base pairs) of DNA or RNA than short-read sequencing approaches (75-300 base pairs). LRS has particular advantages for certain applications, making accessible some otherwise hard to sequence parts of the genome. With support from the WYNG Foundation, we investigated the main issues with clinical LRS.

Although genomic medicine is now advancing rapidly, in many cases clinicians are still unable to definitively pinpoint the underlying cause of a suspected genetic disease. An accurate diagnosis is essential to guide care for patients and to understand the risks of other family members being affected by the same condition.

For this reason, there is considerable interest in how far LRS could improve clinical genomic testing, notably by enhancing the detection and interpretation of more complex genetic changes that could cause rare diseases. This includes the ability to sequence and analyse larger structural variants in DNA, and to resolve inheritance patterns of variants by determining whether they are present on the same or different copies of a gene. These approaches could also be beneficial in cancer genomics, helping to identify the critical mutations that drive tumour progression and spread.

A further area of potential for LRS is enabling analysis of other valuable 'omic information, by unravelling non-coding DNA modifications (epigenomics) and improving RNA sequencing data (transcriptomics). Such data could have considerable value for analysis of complex cancer genomes, especially when generated through real-time sequencing approaches.

Long-read sequencing has promise, but it has limitations, such as requiring a high DNA sample quality and producing a generally lower throughput, at higher cost. Further clinical validation is also needed. Our research shows that LRS is likely to complement rather than replace short-read sequencing for genomic testing in the future.



#### Advancing precision medicine

As our understanding of cancer genomics advances, targeted cancer therapies that offer more precise and effective action against tumours are emerging. These include a new class of 'tumour agnostic' or 'histology independent' therapies that can be used against the same genetic features of cancer that might occur in very different types of tumour.

Moves towards a 'genomics first' approach to cancer testing and treatment should help patients access precision medicine, by using the genomic features of each tumour to inform treatment options from the start.

Roche Products Ltd sponsored us to research the policy issues posed by the use of tumour agnostic medicines and genomic testing in the NHS, and identify any barriers to clinical uptake and patient benefit.

In discussion with laboratory, clinical and patient experts, we found strong agreement that first-line genomic testing of tumours could widen access to the best treatment option for each patient. Patients with rarer cancers, where the only treatment options may be very new therapies, could benefit but also patients with more common cancers in whom targeted therapies, especially if used as first-line treatments, could also be effective,

Stakeholders felt that plans for genomics-first cancer testing could be strengthened by the development of clear NHS pathways for sampling and testing tumour tissue, and sharing the results of testing. Closer working between health professionals and patient groups is also essential.

One of the greatest concerns expressed is the need to enable genomic testing for both approved clinical and research uses, albeit with a clear distinction between the two types of result and how they would be reported to clinicians.

The valuable consensus recommendations will hopefully drive more equitable access to testing (and the best possible treatment choices and outcomes) for patients across the country, as well as supporting ongoing innovation in precision medicine.

### Data intermediaries

We have a wide-ranging programme of work examining the legal, ethical and regulatory challenges posed by health data collection, storage, sharing and use for research.

One problem is that a relative scarcity of suitably accessible, diverse and well-curated data for research remains a rate-limiting step for health innovation. In 2022, our team examined whether so-called 'data intermediaries' could bypass this bottleneck.

Data intermediaries are a form of data stewardship structures designed to mitigate some of the main risks associated with data sharing. Whilst there is no formal definition of a data intermediary, they are effectively a set of specified relationships between individuals or groups of people and data, set out in a core document. Specific responsible individuals oversee the intermediaries and ensure compliance with the agreed standards and behaviours.

Trusted research environments (TREs), increasingly referred to as secure research environments (SREs) are the closest equivalents in health research. They fulfil many, but not all of, the common criteria for an intermediary, granting use rights and placing limitations on permitted data users. They have enhanced security features and are overseen by those placed in a position of trust to ensure use rights are not breached. For data intermediaries to work effectively for healthcare and biomedical research, trustworthiness will be critical.

Other forms of intermediary such as data trusts and personal information management systems (PIMS) could also add value for research but are as yet untested.

This is undoubtedly an important area of policy. Further investigation into the forms of data intermediary that could be most useful in different healthcare contexts will be essential, as will the ethical and legal boundaries of wider data that intermediaries could collect from individuals to foster further innovation.

## Informing policy

Polygenic scores (PGS), also sometimes referred to as polygenic risk scores, are a topic of intense interest to all those concerned with prediction and prevention of disease.

A polygenic score is calculated from the combined effects of multiple genetic variants associated with a disease; whilst some rare genetic variants may confer a very high risk of disease, most variants linked to common diseases make only small individual contributions to risk. However, if these risks are combined, the overall risk could become significant for some people.

The PHG Foundation has been working on the evidence base for polygenic scores and the practical implications of their potential uses for health for some years. In 2022, we focused on the pressing question of what PGS could mean for cancer prediction, prevention and management.

Cancer is a highly variable and complex disease, and a variety of genetic and non-genetic factors contribute to its development. Risk prediction models that bring together information on such factors can inform effective disease prevention strategies.

Polygenic scores are a measure of genetic contribution to the risk of developing cancer. Could they help inform and improve risk prediction and cancer prevention? In our report for health policy makers and other stakeholders, we set out the evidence for how PGS could help predict cancer risk, and in which circumstances they could help provide more personalised risk prediction.

Although this is looking increasingly feasible for some forms of cancer, this is not the case for all cancers. Moreover, since current tools for risk prediction already vary, the potential for polygenic scores to improve such tools also varies considerably across different types of cancer. Therefore, even if current gaps in evidence of utility are addressed, polygenic scores are by no means a 'one size fits all' solution.

Implementation of risk prediction using PGS will require thorough understanding of their impact on clinical care. Efforts should be focused on gathering appropriate evidence to demonstrate clinical utility. Any moves towards premature use of these new tools could undermine confidence in genetics and risk prediction, and policy makers should proceed with caution, despite the excitement surrounding PGS. The PHG Foundation has produced a series of reports which set out the potential applications of polygenic scores for risk prediction in different contexts, as well as outlining current gaps in the scientific evidence.

#### 77

Genome UK: 2022 to 2025 implementation plan for England UK Department of Health and Social Care, December 2022

### **Engaging communications**

New and potential applications of science and technologies for health and care are becoming increasingly prominent, with news outlets and social media spreading the word about new research, discoveries and trials. However, it can be hard to distinguish the genuine hot prospects from more blue-sky or longer-term thinking - as our own horizonscanning frequently reveals.

Science never stands still, and nor does the PHG Foundation. In recent years we have developed considerable expertise in effective multimedia communications and engagement, enabling us to not only increase our digital presence, but also expand our reach beyond professional stakeholders to the wider public.

Our new Making science work for health podcast series is aimed at this broader audience, featuring PHG Foundation policy analysts who set out the facts around the latest 'hot topics' in and around genomics and health, and explain what these new scientific developments could really mean for patients, health professionals and members of the public.

The first podcast episodes have discussed liquid biopsies for cancer and precision medicine for inflammatory bowel disease, with many more exciting applications to examine in the year ahead.

Of course, our cross-disciplinary policy research and analysis often reveals broader issues and ideas arising from new technologies that merit wider examination. To this end, we also launched a new digital long read series that takes a deeper dive into the implications of science for health and public policy.

The long read on Digital twins considered their potential utility for healthcare; digital twins are virtual avatars created to mirror personal data to predict and model health outcomes for an individual. What could this mean for personalised disease prevention and care?

# The history of genomics policy

Policy - plans and actions supported by laws, regulations or guidelines - is central to the PHG Foundation mission; by providing evidence and insight to inform policy development and influence decision-making, we work to optimise and accelerate the appropriate application of genomics and related science for health benefits.

The historical impact of science on society and on medicine and public health is relatively easily tracked, but the enabling policy is less visible, taking place behind the headlines. Over the past year, we were pleased to support independent research into the history of genetics and genomics policy in the UK. This work was led by renowned historian Sally Sheard, Andrew Geddes and John Rankin Professor of Modern History at the University of Liverpool.

The resulting book, by Dr Phil Begley and Prof Sheard, sets out the discoveries from their research, including witness seminars and interviews, for wider audiences. It focuses on the science-driven NHS transition from clinical genetics (a highly specialised service for patients with heritable genetic disease) to the mainstream genomics services available today for the prediction, prevention, diagnosis and management of a range of diseases.

The development of public health genomics as a discipline encompassing the population health applications of new technologies, as well as the wider policy challenges these presented (such as ethical, legal and societal issues) is highlighted as a critical stage in the evolution of genomic medicine.

Just as scientific innovation is often led by exceptional researchers, the potential impact of relatively small numbers of driven, persuasive and above all visionary individuals on policy is revealed to be considerable. At the same time, the necessity for constructive collaboration across different disciplines and domains to achieve common goals for health is amply demonstrated. 66

Genetics and genomics now have a well-established place in health policy debates and are widely conceived as being central to the future provision of healthcare services

77

Making Genetics and Genomics Policy in Britain: From Personal to Population Health Begley P and Sheard S Routledge, September 2022

### Governance

As a linked exempt charity of the University of Cambridge, we are proud to have a distinguished group of trustees providing support and strategic oversight to help us deliver our mission:

- Prof Patrick Chinnery Head of the Department of Clinical Neuroscience, University of Cambridge
- Prof Nita Forouhi Professor of Population Health and Nutrition, University of Cambridge
- Dr Anthony Freeling Acting Vice Chancellor, University of Cambridge and former President of Hughes Hall
- Mr Andrew Hutton Director, AJ Hutton Ltd
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- Prof Liba Taub Professor Emerita of History and Philosophy of Science, University of Cambridge and Director of Research at the Whipple Museum of the History of Science
- **Dr Ron Zimmern** Founder and Chairman of the PHG Foundation

### Finances

The PHG Foundation is funded by philanthropic donations, primarily from the Hatton Trust and the WYNG Foundation. We are not funded by the University of Cambridge. Other income comes from grants, collaborations, and commercial and public sector consultancy. We also have a modest investment portfolio. Most of our spending is on charitable activities, which includes our work programme and staff costs.

#### 2021-2022 income: £1,215k



### Publications

In addition to peer-reviewed papers for academic journals, over the last year we published an essential policy report on polygenic scores for cancer, as well as several consultation responses, policy briefings and reports for partner organisations. A selection of these outputs are shown opposite.



We were also pleased to see one of our previous policy briefings, RNA vaccines: an introduction (by Head of Science, Dr Laura Blackburn) reach over one million views on our website.

Originally produced in 2018, this briefing described the scientific background and medical prospects for the new (and then relatively obscure) concept of RNA vaccines. The COVID-19 pandemic ignited interest in this area.

Whilst the science of RNA vaccines has moved on, the value of considering the policy implications of potential game-changing technologies well in advance - and producing accessible explanations - is clearly demonstrated by this example.

Our formal publications are supported by a range of other digital information products available from our website and media channels. In 2022, these included new static and animated explainers on environmental human genomics and digital twins.















PHG







# People







































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