Medical Research Council

MRC Unit and Centre Portfolio Review

Main Panel Report

Contents

This report provides a high-level view of research and health needs and opportunities over the next decade as discussed and agreed at the Main Panel meeting of the Medical Research Council (MRC) Unit and Centre Portfolio Review. Informed by existing MRC and other funder strategies and considering national and global health perspectives, including the response to and potential impacts of the COVID-19 pandemic, the review aimed to identify where unit, centre or equivalent investment could maximally benefit human health and transformationally contribute to UK leadership in the medical research. It further sought to consider how reshaping the existing unit and centre portfolio, if merited, would enable it to better respond to or add value to this agenda. Recommendations were provided by an independent panel of leading UK and international experts, including representatives from the review's three Domain Panels (see Annex 1 for a list of members).

Executive summary

The Main Panel commended the work of the review's three Domain Panels (see Annexes 2, 3 and 4 for the Domain Panel reports) and agreed that they had identified important shared themes that will require interdisciplinary and cross-sectoral approaches to deliver.

The panel agreed that there is a significant research opportunity in the development of new tools and technologies able to provide quantitative measurements across temporal and physical scales, and to perturb biological systems, with spatial and temporal precision, to probe mechanisms and causality. Members agreed that there needs to be a reinvigoration of the integrative physiological skills base, to ensure that reductionist (molecular, genetic) approaches can be linked to higher organisational levels (cell, tissue, organ, organism, population), with integration across systems. This will be critical for extrapolating from genetic discoveries, for teasing out commonalities and shared genetic and mechanistic pathways across multiple conditions, and for understanding the drivers of multimorbidities and the impacts of ageing.

The development of large and rich datasets (omic, health and administrative) and the means to integrate and analyse them provides us with a step-change opportunity to better protect and extend the health of the population. The panel agreed that this would require a greater emphasis on taking fundamental insights into intervention and implementation at scale, and an Institute of Public Health Intervention and Improvement, engaging across UKRI councils, had significant attraction. It would be able to create the necessary multidisciplinary and intersectoral research environment to exploit the full potential of these new data opportunities.

Data is a shared priority across the domains and is necessary for the delivery of all the ambitions described above. The panel agreed that the UK's ability to exploit the opportunities presented by data-driven approaches is currently significantly curtailed by a shortage in required expertise. Members recommended that addressing this shortage would require engaging existing cross-disciplinary expertise strengths and the development of a new cadre of experts; the training of these experts could benefit from a new model in which trainees and practitioners hold joint appointments in a substantive science unit or centre and in a geographically dispersed health data science methods entity.

The panel agreed that priority health needs include those driven by the impact of anthropogenic change, including: environmental change, such as climate change, urbanisation and pollution, and infectious disease risks, such as pandemics, transfer between species and antimicrobial resistance (AMR); healthy ageing, where we are in a position to understand the cellular mechanisms driving ageing; and mental health, where new opportunities and insights provide potential traction against the significant burdens it poses across the life-course.

Addressing these opportunities and needs will require a new generation of interdisciplinary researchers able to exploit new opportunities with agility, prepared to take risks with their research, equipped to translate their work and able to produce robust and reproducible data.

The panel agreed that the current portfolio of units and centres has enormous strengths and has made important contributions. Nevertheless, there are clear opportunities to improve impact. These include: improved integration, both within the portfolio, to tackle shared challenges, and on key health issues; increased collaboration with other councils, medical charities, the National Institute for Health Research (NIHR) and industry; strengthening the portfolio's sharing culture and capability, with the units and centres being national assets that set standards in the quality and impact of their work and in open science; and enhanced agility.

The panel noted that none of the current portfolio is supported in partnership with other UKRI councils. This contrasted strongly with its observation that addressing the panel's prioritised research opportunities and health needs will require rich collaboration across the breadth of UKRI research. In addition, a strengthened interface with NIHR is required, links with industry need to be deepened and broadened, and patients, the public and policymakers should be engaged in the co-production of research questions.

1. Introduction

The MRC Unit and Centre Portfolio Review Main Panel was established to draw together the recommendations made by the review's three Domain Panels (Molecular and Cell, Physiological Systems, and Population and Public Health), MRC Board and Overview Group comments on the Domain Panel recommendations, and university and MRC institute contributions, so as to:

- identify priority research and health opportunities and needs over the next five to 10 years where unit, centre or equivalent investment could transformationally provide maximum impact and contribute to UK leadership, having first considered whether any key opportunities or needs have been missed by the review process
- recommend key areas that MRC may wish to focus its efforts on in the short term regarding its existing portfolio, to better address the medium- and longer-term opportunities and needs
- agree the key enablers and partners that MRC will need to work with, to address identified opportunities and needs.

2. Prioritised areas of opportunity and need

The Main Panel commended the Domain Panels on their reports, which provided a comprehensive picture of key opportunities and needs with the following important shared themes:

2.1 Research themes

Tools, technologies and measurement

In order to better understand biological systems, we need analytical tools and technologies able to provide quantitative measurements across temporal and physical scales, from the molecular, through cells, tissues and physiological systems, up to whole organisms and individuals. This requires state-of-the-art infrastructure and staff, to interrogate and integrate omics and functional readouts, and the development of new technologies, including imaging modalities, methodologies and mathematical approaches. Such developments have great potential in both research and clinical and diagnostic applications and would benefit from being informed by clinical needs. The panel agreed that shortcomings in current capabilities in this area had hindered our ability to respond to the diagnostic and clinical characterisation challenges that the emergence of COVID-19 has posed.

In addition to improved analytical technologies, members agreed that there was a need for tools and approaches to perturb biological systems, with spatial and temporal precision, to probe mechanisms (of both health and disease) and causality. Chemical biology was regarded as having potential here, but members agreed that this field would benefit from improved communication and collaboration between disciplines, investigators and research councils. The panel agreed that the emergent ability to synthesise whole genomes offers the potential to interrogate and perturb systems with a precision and scale not previously possible.

While the panel agreed that existing investments at the interface between biology and the physical sciences, such as the Rosalind Franklin Institute (RFI), have the potential to make valuable contributions here, the opportunity and the need were deemed to be greater than the RFI could address alone, with the need for a £100 million-plus investment considered.

Integrative physiology

Members agreed that UK capability in physiology research has waned over a number of years and is hindering our ability to extrapolate from genetic discoveries, deliver a comprehensive understanding of physiological function, and translate into application. This requires working across scales and experimental medicine approaches, to ensure that reductionist (molecular, genetic) approaches are linked to higher organisational levels (cell, tissue, organ, organism, population), with integration across systems. The latter would be particularly important for teasing out commonalities and shared genetic and mechanistic pathways across multiple conditions, and for understanding the drivers of multimorbidities and the impacts of ageing.

The panel agreed that addressing this challenge will require a focus on training and career development, with many universities having closed their physiology departments and with investigators in the field being near the end of their careers. Members agreed that a networked approach may be preferable to a stand-alone unit model to meet this need, and that not addressing it will damage translation out of discovery science. This translation benefits from contact with the clinic and the means to drive observations through to clinical applicability, the latter requiring an increase in the translational skills base, in experimental medicine work and in industrial partnership.

Interventional population health

The establishment, through significant investment, of large and rich datasets (omic, health and administrative) and the development of new tools and methodologies able to integrate and analyse this data provides us with a step-change in our ability to better protect and extend the health of the population. This includes opportunities in addressing hitherto intractable issues such as socio-economic, cultural and regional differences. It is, however, not sufficient to merely understand the causes of such differences. A greater emphasis is needed on taking fundamental or more applied insights into intervention and implementation, at scale, for population health benefit.

A challenge-led approach could help coalesce the required disciplines and expertise, not just from the biomedical and health sectors but also from other important contributors; these include sister UKRI research council communities, government departments, Public Health England and its devolved administration equivalents, and local authorities. While a network of distributed investments could help, an institute without boundaries bringing groups who have historically not worked together into proximity to address a shared challenge has significant attractions. This proposed institute would operate best through a single-site or hub-and-spoke model. It was agreed that this initiative would complement rather than compete with Health Data Research UK (HDR UK), drawing on the improved access to data that the HDR UK platform provides, while greatly enhancing the impact of this data through its focus on intervention. With a central objective to drive implementation science, this institute should have a rich interface with downstream stakeholders (patients, the public and policymakers).

Data

Data are a shared priority across the three domains and is necessary for the delivery of all the ambitions described above. Optimal use of data requires infrastructure, technology and expertise in gathering, curation, sharing, integration and analysis, across multiple sources. The latter requires developments in bioinformatics and modelling, including temporal and causal inference methods, and visualisation.

Members observed that barriers to data-sharing across the health system that have acted as in impediment to the field for over a decade have been largely resolved to address the challenge posed by COVID-19. Members strongly advised that MRC, acting collaboratively through UKRI and with other sector partners, HDR UK and NIHR, should seek to ensure that these barriers do not re-emerge once the pandemic has been curtailed. In addition, members recommended that strengthened connection is needed with the private sector (such as the digital industry, social media and retail companies). This will require careful consideration of new partnering models. Existing models developed for biopharma may need to be amended, given the unique value of the NHS and associated data and the speed and cost of commercialising this data, relative to the lower value of non-commercial assets and high costs of drug development.

The panel agreed that the UK's ability to exploit the opportunities presented by data-driven approaches is currently significantly curtailed by a shortage in required expertise. Members recommended that addressing this shortage would require new approaches to engaging existing cross-disciplinary expertise, such as the involvement of mathematicians and mathematically literate biologists and clinicians, and would necessitate the development of a new cadre of experts. This new cadre will need to be trained in and combine an understanding of computing, statistics and molecular, physiological and population health domain-specific knowledge. This training could benefit from a new model in which trainees and practitioners hold joint appointments in a substantive science unit or centre and in a geographically dispersed health data science methods entity. This would ensure that researchers would be not only coalesced around a specific health or science challenge but also part of a wider like-minded community that would share ideas, drive collaborations and support wider ambitions in skills, capacity and career development. This community would require strong intellectual leadership and direction, and a supportive and fertile intellectual environment.

2.2 Health themes

The panel considered the Domain Panels' recommendations on pressing health needs and agreed the following priorities, with more detail on each available in the accompanying Domain Panel reports:

Anthropogenic change

The impact of anthropogenic change, including environmental change (such as climate change, urbanisation and pollution) and infectious disease risks (such as pandemics, transfer between species and AMR), was a priority concern in all the Domain Panel reports. Tackling these changes will require bridging from the molecular through to broad societal issues. The panel recommended that this should be a key area for MRC and requires concerted and careful cross-council consideration and action, with a clear challenge-led focus.

Healthy ageing

We sit at a juncture where we can understand the cellular mechanisms driving ageing, which could provide targets for therapeutic intervention, and where improvement in life expectancy in the UK and a number of other developed countries is faltering. To both exploit the opportunities and mitigate the risks, we need to take a life-course perspective and address the issue of keeping separate the study of healthy ageing, including prevention, and the study of diseases of age, which in the view of panel members has been an impediment to the field. Rather than focusing on individual diseases, members recommended that examining cross-cutting aspects, such as inflammation, fibrosis, chronobiology and the microbiome, may be beneficial. This approach also talks to the challenge of multimorbidity.

In studying ageing, members recommended that consideration should be given to the examination of resistance and resilience. While we tend to focus on those outliers who are suffering extreme disease, there is also much to be learnt from those who maintain extreme health in the face of genetic, social and environmental challenges.

Mental health

Mental health was recognised as a priority area due to the significant burden it poses across the life-course, and because new opportunities and insights (spanning genomics, imaging, systems neuroscience, neuroinflammation and data-driven epidemiology) make it potentially more tractable. Notwithstanding that, breakthroughs will require real inspiration and concerted multidisciplinary and cross-sector action.

To address these needs, members agreed that investments might be configured around individual diseases, cross-cutting issues, or fundamental mechanisms. The current unit portfolio does not have a significant emphasis on disease challenges, which in part may be due to these having been a focus of the medial research charities, and members agreed that bringing experts together with an ambition to tackle a disease or systemic issue could be of value. However, it was cautioned that it remains critical to provide long-term support for fundamental investigator-led research addressing the key questions underpinning biomedical science.

The panel agreed that challenge-led centres of excellence offered strong routes to coalesce interdisciplinary skills and effectively drive knowledge from discovery science into application and health benefits. Members noted that large-scale, challenge-led approaches had been used more in the physical than the biomedical sciences, but that they could provide an opportunity. Members noted that, post-COVID-19, MRC may need to take a more challenge-led approach to pandemic infections, including addressing inequalities and health, and likely requiring stronger collaboration between institutes, units and centres.

2.3 Delivery models

Given that multiple disciplines will need to be brought together to address the identified opportunities and needs, virtual institute and virtual unit models were seen as being of potential merit. Such institutes and units must be research organisation agnostic, standing apart from universities in their vision but working closely with them in underpinning areas of common interest. Members agreed that the ethos of such a national entity was more important than whether it adopted a hub-and-spoke model or a network model, or had or did not have a physical presence.

2.4 Training and careers

Addressing the opportunities and needs described above will require a new generation of interdisciplinary researchers who are able to exploit new opportunities with agility and are prepared to take risks with their research, are equipped to translate their work and are able to produce robust and reproducible data. These researchers, and equally-needed career technologists, will have to be adept at working in teams and be provided with supportive career paths that recognise and champion the multiple contributions they will make.

3. Opportunities and implications for the existing portfolio

The panel agreed that the current portfolio has enormous strengths and had made important contributions. Nevertheless, there were clear opportunities to improve impact:

Integration

Members agreed with Domain Panel reports that greater integration of the existing portfolio was needed, both with each other, to tackle shared challenges, and in terms of addressing key health issues. This would likely require targeted investment to incentivise cross-fertilisation and enhance coordination and capability in areas of common interest, including tackling underpinning disease mechanisms (such as fibrosis, inflammation and microbiome). It would also help strengthen multi- and interdisciplinary approaches to tackling the biggest science and health challenges, and collaboration with other councils, medical charities, NIHR and industry. Our portfolio should also link better with non-traditional disciplines (such as mathematics and engineering) to pursue ambitious, multidimensional programmes. Increased dialogue with the clinic is also needed to better inform research endeavours and to help drive observations through to health improvements. While the investment in the Africa units shows a commitment to working in low- and middle-income settings, members recommended that it is important that their work is more closely connected with that of the other institutes, units and centres, for mutual benefit.

Outward-facing and open science

The units and centres should be national assets, setting standards in the quality and impact of their work and in open science, to drive collaboration and public trust. They should be transparent hothouses of discovery and application with a strong sharing culture and capability, both between themselves and with the wider community, which should embrace the proactive dissemination of tools, data, technologies and methods.

Agility

Members expressed concerns that the nature of research objectives used in the unit and centre quinquennial review process and a lack of challenge-led approaches might curtail unit and centre agility, while acknowledging their rapid response to the threat posed by COVID-19.

Interventional population health

The panel noted the excellent work of MRC's population science investments and the underpinning strengths of the UK's population cohorts, but agreed that there was a need to move further towards turning insights in determinants of population health into effective population-level interventions. Members agreed that the response to COVID-19 had highlighted a lack of interventional capacity within existing units, which have generally focused on understanding long-term exposures rather than health protection and prevention. Nonetheless, the panel recognised that the current portfolio provides potential synergies with the proposed interventional population health institute.

4. Enablers

UKRI

The panel noted that none of the current portfolio is supported in partnership with other UKRI councils. This contrasted strongly with its observation that addressing the panel's prioritised research opportunities and health needs will require rich collaboration across the breadth of UKRI research. Examples include the need to work closely with BBSRC, EPSRC and STFC to deliver on ambitions in tools, technologies and measurement, integrative physiology, and data, and with AHRC, BBSRC, EPSRC, ESRC, and NERC to deliver on ambitions in anthropogenic change, mental health and interventional population health.

Members cautioned, however, that MRC should not underestimate the challenge of bringing different disciplines together. Experience from the biomedical and engineering interface suggests that this will require the deployment of a clear strategy, developed with partner councils, over at least a 10-year time period. Such a strategy might start by developing areas of existing expertise before moving to more substantive funding. Members recommended that co-localising teams with co-supervised PhDs can greatly help in developing a shared language and values, needed to drive truly integrative science.

NIHR

Panel members agreed that partnership with NIHR is critical but that this relationship needs strengthening. While the Occupational Safety and Health Consultants Register (OSCHR) had provided effective coordination at this important interface on its foundation, the view from those with links to the Biomedical Research Centre was that this interface has weakened in recent years, and that differences in organisational structures between MRC and NIHR appeared somewhat inhibitory.

Charities

The panel reflected that the financial pressures which the medical research charities face due to COVID-19 may create pressure for MRC to take a more disease-focused stance, although members extolled the need for continued support of fundamental science. Members further recommended that plans in the areas of infections, mental health and climate change will need to take due consideration of Wellcome's strategic intent in these fields.

Industry

The panel noted a lack of strategic connectivity with the Innovate UK (IUK) catapult network and recommended that strengthened links were needed spanning the biopharmaceutical, medical device, diagnostic and digital industries. These links would provide access to complementary expertise, resources and data and strengthen routes to impact and commercialisation.

Patients, the public and policymakers

Members supported a participatory approach that encourages co-production of research questions with patients, the public and policymakers. This can help to ensure that research evidence addresses individual and local as well as global priority challenges, as well as to manage research risks and support outputs becoming impacts.

5. Annexes

- **Annex 1: Main Panel membership**
- **Annex 2: Molecular and Cell Domain Panel report**
- **Annex 3: Physiological Systems Domain Panel report**
- **Annex 4: Population and Public Health Domain Panel report**

Annex 1: Main Panel membership

Main Panel

- **Chair: Professor Dame Nancy Rothwell**
  (University of Manchester)
- Professor Albert Hofman
  (Harvard TH Chan School of Public Health)
- Professor Sir Alex Markham
  (University of Leeds)
- Professor Dame Anne Johnson
  (University College London)
- Dr Jason Chin
  (MRC Laboratory of Molecular Biology)
- Professor Linda Partridge
  (Max Planck Institute for Biology of Ageing)
- Dr Neil Thompson
  (HealX)
- Professor Nyovani Madise
  (African Institute for Development Policy)
- Professor Patrick Maxwell
  (University of Cambridge)
- Dr Raj Parekh
  (Advent Life Sciences) *Apologies*

Molecular and Cell Domain representatives

- **Domain Chair: Professor Doreen Cantrell**
  (University of Dundee)
- Professor Mike Malim
  (King's College London)
- Professor Peter Parker
  (King's College London)

Physiological Systems Domain representatives

- **Domain Chair: Professor Jonathan Weber**
  (Imperial College London)
- Professor Ian Hall
  (University of Nottingham)
- Professor Jane Norman
  (University of Bristol)

Population and Public Health Domain representatives

- **Domain Chair: Professor Dave Leon**
  (London School of Hygiene and Tropical Medicine)
- Professor Cathie Sudlow
  (University of Edinburgh)
- Professor Peter Diggle
  (Lancaster University)

Annex 2: Molecular and Cell Domain Panel report

This report provides a high-level view of research needs and opportunities over the next decade within the Molecular and Cell Domain of the MRC Unit and Centre Portfolio Review. Informed by existing MRC and other funder strategies and considering national and global health perspectives, the review aimed to identify where unit, centre or equivalent investment could transformationally contribute to UK leadership and to consider, if merited, reshaping the existing unit and centre portfolio, to better respond to or add value to this agenda. Recommendations were provided by an independent panel of leading UK and international experts across the domain (see Annex 1).

Executive summary

With recent developments in research tools, technologies and equipment and advances in data science the 21st century presents a key opportunity to move into a 'post-genomic era' (that is, all levels beyond the genome, such as lipids, glycans and metabolites). This would involve capitalising on the advances made in the 20th century's 'genomic era', to move into a mechanistic understanding of dynamic fundamental processes that would deliver step changes in understanding human biology and addressing key health areas to drive forward clinical benefits to society. In this context, the review identified two challenges: environmental change and infectious diseases; and healthy ageing.

This review identified an overarching challenge-led opportunity: **"to understand, in a post-genomic era, the mechanisms by which molecules, cells and tissues work as dynamic biological machines, to improve health and treat disease"**. To deliver against this opportunity, the review identified priority needs in developing methodologies, technologies and probes to better observe and quantify molecular and cellular heterogeneity, complemented by developing novel chemical and bio-inspired tools and interventions; such tools and interventions would be designed to actively perturb cellular and tissue systems to reveal functional significance of variation, as well as pathways and networks of biological processes. Maximising mechanistic insights from data generated by such observational and perturbational approaches would require modelling, curation, sharing, training, informatics and better data visualisation.

To support this, it would be critical to ensure strong academic-clinical interconnectivity enabling strategies to translate fundamental science discoveries to the clinic. Cultural transitioning was also a priority, towards building institute, unit and centre hothouses of technology development, discovery and 'distributable' molecular science and methodologies. To deliver and sustain these priorities would require consideration of longer-term director-led funding models, and potentially large challenge-led investments (the challenges to be defined by the community) that draw together key interdisciplinary capabilities across the biological, physical and chemical sciences.

1. Developing the list of key areas of opportunity and need

The following provides a summary of the key outputs from the panel discussions covering the dimensions set out in the review's terms of reference: scientific development, national research capability (such as platforms and resources) and accelerated impact.

A. Threats and challenges to sustaining and improving health

Dynamic and changing environments

The panel identified health impacts due to the changing environment as a key challenge, in the context of both infectious and non-infectious threats. A particular threat was around 'pathogens crossing boundaries', both across species and across geographic domains, with drivers due to the changing global environment (such as impacts on the food chain) and behavioural changes (both human and animal). Such changes in patterns of infection could be aggravated by co-threats posed by sources of non-communicable exposure such as toxins (microplastics, for example) and pollutants, with impacts on susceptibility to disease of vulnerable groups. 'All pollutant' studies should move beyond air and include changes in nanoparticles. These threats pose challenges across the UKRI spectrum and demand improved pre-emptive measures, such as a focus on animal health to decouple animal-human infectious agent transfer. The panel identified opportunities for applying cutting-edge genomic and epigenomic technologies to more effectively assess and track who is susceptible, who gets infected, and why, and to monitor infectious disease spread by following asymptomatic as well as symptomatic individuals, thereby enabling targeted protection of vulnerable individuals.

To protect against emergent infections, the panel discussed capitalising on the development of effective in vitro and in vivo models including in silico modelling and 'big data' systems, and therapeutic banks and archives. An important need was the extensive cataloguing and curating of micro-organisms of pathogenic potential, such as compilation of known viral protein structures for use in developing small-molecule interventions. As well as targeting bacterial pathogens, there needs to be a focus on fungal pathogens.

Healthy ageing

We lack knowledge of the normal ageing process, including understanding of brain ageing and senescence in the immune system. Ageing changes the cellular and tissue response (for example, regenerative capability, drug metabolism and biology) and molecular and cellular functions. The panel highlighted the need to better understand the mechanisms by which healthy versus 'unhealthy' ageing occurs in terms of prevention, and the opportunities that exist for 'resetting' the ageing process to improve 'health-span'. This will require an understanding of the ageing and repair process at different levels (molecular, cellular and tissue; for example,, brain regions entering hibernation followed by synaptic regeneration) to identify causal mechanisms.

Understanding malfunctioning neurons in neurodegeneration and ageing needs to move beyond a focus on causality through genetics and quantitative trait locus studies, and relatively simplistic molecular pathology (such as autosomal-dominant production of protein aggregates), to capture changes in other molecule types (proteins, lipids) and systems (mitochondrial malfunctioning) at multiple organisational levels.

Better understanding of ageing requires the development of fit-for-purpose experimental systems (animal and advanced in vitro models). Current preclinical models often use young animals or induced pluripotent stem cell (iPSC) or organoid systems to model diseases of lifestyle and ageing, such as obesity and cancer, that do not take account of age. Using such models to assess efficacy of a potential drug or advanced therapy may then contribute to clinical-trial failures

Lifestyle and diversity

The panel discussed the important role of lifestyle factors for health, including socio-economic factors in areas such as mental health, addiction and self-harm, and the potential roles of social and ethnic differences in diet and microbiome, with the opportunity of using new monitoring and sensing approaches to measure impacts of diet on the microbiome in individuals in real-time. 'Modern' health issues were also discussed, including potential changes in the immune response due to sterile environments, and their impacts on allergies.

The panel also discussed multimorbidities, noting the need for better understanding of drivers behind co-morbidities, for example mental health with or without dementia, and noting that multimorbidities are increasingly seen in the young.

The panel identified the need to better recapitulate human diversity in experimental systems (animal and advanced in vitro models) and clinical drug trials. This included the need for adequate analysis of the impacts of sex difference and consideration of the impacts of circadian rhythms on infection and drug pharmacokinetics. It was recognised that there was a need to consider ethnic diversity in experimental medicine and clinical trials and here the importance of global interactions was recognised. This will require researchers and clinicians to work more closely with relevant communities, recognising the key need for public engagement and cocreation (such as to address anonymity and choice issues) to develop, for instance, more representative clinical trials (to avoid, for example, big mismatches in early-detection screening trials in local populations where, say, 50% of the population is from an ethnic group but only 2% are engaged).

B. Research innovations and opportunities to develop fundamental new insights and/or address identified health challenges

Understanding biological heterogeneity

A key area of opportunity was better understanding of variation. This ranges from human genetic diversity, with emphasis on precision sex or ethnicity difference and opportunities afforded by whole genome sequencing (WGS) data from the NHS, through to molecular, cell and tissue heterogeneity, in time and space. The aim would be to better understand the linkage of variation to healthy and diseased states. Environmental influences on variability, such as host-pathogen interactions and the microbiome, were also identified as important, as well as the impacts of mechano-dynamics on cells and tissues. There was recognition of the need to understand the impact of genetic diversity on biological phenotypes (that is, how genome variation translates to phenotypic impact).

Measuring: methods, tool development and model systems

To capitalise on and move beyond the 20th century's 'genomics era', there were seen to be opportunities to discover and explore 'what we don't know or poorly know', such as single-cell analytics in situ and in real-time, quantification of omics data, and exploration of the 'post-genomic' world including ribonucleic acid (RNA), lipids and membranes, glycomics, protein post-translational modifications and metabolites. Delivering these ambitions will require new methods and tools, requiring strong integration of physical sciences and presenting major

opportunities in artificial intelligence (AI) and computational biology, non-invasive imaging, biosensors and technologies for cell and tissue manipulation. Pertinent to the above, the panel also identified key skills gaps and needs in AI and mathematical modelling.

These studies would be supported by development of sophisticated in vitro models, such as advanced culture systems and exploitation of biodiverse models from different species, with a critical need for the validation of such models and the agreement of definitions and standards across the scientific community.

C. Accelerating impact and infrastructure

Equipment

There is a need for much better funding for infrastructure to support discovery science. This includes support for:

- for-sale, off-the-shelf equipment, potentially hosted in centres providing state-of-the-art capabilities and critically associated data infrastructure and human skills (for example, mass spectrometry and high-resolution imaging equipment)
- the development of new methodologies and tools (developing tools 'you can't buy' requires long-term support and can benefit from industry engagement, thereby providing both scientific and economic benefits).

Such developments could address key needs in the dynamic understanding of spatial and temporal arrangements and interactions of molecules with respect to each other. There is also a need for technologies for single-molecule tracking. The panel identified needs for early detection and risk stratification, which will require sensitive non-destructive and minimally invasive longitudinal metrological (4D) approaches, able to be applied in real-time and across scales.

To enable these capabilities, there is a need for better support and for career paths for critical team members (career technologists) with the skills and expertise required to provide equipment, specific support and data interpretation.

Data

The panel identified needs in data curation, storage, access, metadata, sharing and synthesis. Members agreed that bioinformatics should be embedded in biological programmes, so as to be informed by them. In turn, however, it was recognised that there are rich opportunities for bioinformatics and modelling to challenge prevailing biological perspectives. As models can be well ahead of the biology, there is a need to be able to close the gap through validation of predictions. To support modelling, greater quantification of source data inputs (such as numbers of molecules and rates of flux) is required. The panel also noted challenges in visualising biological complexity, the human mind being only able to simultaneously envisage a maximum of around four to five elements.

Infrastructure is required to facilitate working across data sources with appropriate 'big data' quality controls. Such infrastructure would help catalyse partnerships capitalising on key data analysis investments, such as the Alan Turing Institute and the Big Data Institute at Oxford. Rather than moving data between places, the panel favoured moving 'bots' to the data, especially given the constraints of the General Data Protection Regulation (GDPR). It was proposed that data-sharing could benefit from some form of incentivising transactional site (an 'eBay' for data) where one could search, find and access data sources, with the site recording which data sources have been used and how much, rewarding the sharer according to usage.

The panel agreed that delivering all this will require significant capacity development and sustained career support for data scientists. Meeting this need is being made all the harder by the difficulty of retaining trained staff, whether in academia or the pharmaceutical industry, in the face of the lure of the commercial and financial sectors. Overcoming this challenge may require the development of new partnering models with commercial players (such as Google and Microsoft).

Resources

The panel agreed that, as a high priority, there is a need for novel chemical biology probes to explore and map biological processes and for translation to support target validation studies. There is also a need to develop and promote new experimental strategies to perturb molecules in order to understand their functional relevance to biological systems.

Translation

In addition to highlighting the importance of experimental medicine, the panel identified translational bottlenecks and opportunities, including needs for platforms for early-stage drug discovery and target validation, and for tools to probe and validate function and targets and to deliver rapid response, as well as opportunities in drug repurposing, traditional medicines and unravelling the complexities (safety and efficacy) of polypharmacy.

2. Longlist of key areas of opportunity and need

Drawing on perspectives from across the three themes (A, B and C above), the panel developed and agreed a longlist of areas of opportunity and need in the molecular and cell domain over the next decade (see Table 1)[1].

Table 1: Longlist of key areas of opportunity and need identified by the panel

Area of opportunity or need	Comments
How molecules, cells and tissues function as machines	■ Moving 'beyond the genome' to lipids, metabolites, post-translational modifications: who, what, when, how? ■ Cell and tissue complexity and heterogeneity: need for real-time, dynamic, spatial and quantitative metrology ■ Causal outcome pathways (from molecular to population) to study emergence at scale for mechanistic discovery research ■ Quantitative biology of complexity: quantifying imaging and cryogenic electron micrography (CryoEM) data to understand molecule numbers for 'overexpression' ■ Imaging in complexes: the dynamic interactome
Precision and tailored biology	■ Preclinical and clinical approaches to capture diversity (ethnicity and sex) ■ Genetic code: role of 20th century tool in the 21st century ■ Personalised mechanism
The ageing process	■ Healthy ageing ■ Immunosenescence ■ Better models and clinical trials
Changing environmental impacts on health	■ 'Changing environment': adaptation and mitigation ■ Impacts of all pollutants (beyond air) and toxins (such as nanoparticles) on biological processes linked to health and disease ■ Host-pathogen interactions and pathogens crossing boundaries ■ Better anticipatory strategies ■ Changing patterns of vectors
Equipment	■ Off-the-shelf: national infrastructure, data and skill needs ■ New: 'what can't you buy?'; needs long-term support and opportunities for industry engagement ■ Longitudinal metrology (4D): real-time, across scales, non-destructive, minimally invasive ■ To enable early detection; links with risk stratification as you would only look to detect in high-risk population ■ Funding sources for large equipment and how you keep it running with the right key staff (career technologists) ■ Need for centres with complex state-of-the-art integrated equipment with 24/7 expert staff support, for national research needs but also playing a role in setting standards, comparing platforms and so on
Data	■ Need for standardisation; not all working on our own models ■ Infrastructure: curation, storage, access, sharing, metadata ■ People: reward and collaboration, training, embedding in both biomedical and biostats, retention and career paths ■ How to support code development and sharing to support robust tools and reduce duplication? ■ Need for good user interface for the biologist ■ Analytics: quantitative, modelling, data visualisation
Resource needs	■ Chemical biology: biosensors to better understand biology, tools to perturb systems to causally link to function; bioinspired tools that pave the way for target validation ■ Model systems (such as advanced cultures) but with pre-eminence of experimental medicine ■ Access to resources: outward-looking units and centres with capability to share; having technology locally means people train on it ■ Models: needs standardisation and not all working on own models
Translational bottlenecks and opportunities	■ Key: how to rapidly link discovery to experimental medicine? ■ Validated tools to test pathways; target validation ■ Rapid-response platforms ■ HT chemical and CRISPR high-content screens ■ Drugs: repurposing, traditional medicines, unravelling polypharmacy
Synthetic biology	■ Frontier-science opportunity: potential for tools and therapeutics

1 The list was not restricted by whether the areas would or would not benefit from unit, centre or equivalent investment.

3. Prioritised areas of opportunity and need

The panel agreed an overarching challenge-led opportunity **"to understand, in a post-genomic era, the mechanisms by which molecules, cells and tissues work as dynamic biological machines, to improve health and treat disease"**. Priorities to deliver this are set out below:

Developing methodologies, ground-breaking physical and chemical technologies and novel probes to sense, monitor and quantify molecular and cellular heterogeneity in space and time. At the molecular level, there are needs for enhanced measurement of how molecules ('post-genomic': glycans, lipid, metabolites) and proteins interact dynamically (dynamic interactome), and for quantitative analyses (for example of post-transcriptional modifications of molecules and measurements of flux). At the cellular and tissue levels, opportunities exist to capitalise on single-cell quantitative analysis, mechano-dynamic approaches and improvements in the spatial sensitivity of imaging, to study tissue heterogeneity, including of rare founding cells and cellular events in health and disease. These are essential for improved understanding of normal biological processes and molecular pathologies, supporting early detection and interception.

Developing novel chemical and bio-inspired tools and interventions that perturb systems to reveal functional significance of variation and pathways and networks of biological processes. While still capitalising on 20th century 'genomic' tools (such as knockouts and knock-ins) and more recent genome editing, we need to develop 21st century 'post-genomic' tools. These 'perturbagens' include chemical biology tools and bio-inspired tools, such as small interfering RNA (siRNA) systems and protein knockdowns (such as proteolysis-targeting chimeras or PROTACS), with key opportunities for frontier-science synthetic biology, for example to introduce engineered molecular and sub-cellular modules to perturb function. Tools will also be required to perturb intracellular metabolism and must be able to be delivered with both temporal and spatial (intra- and intercellular and tissue levels) refinement, to enable the identification of causative molecular machines, chains and networks and the study of emergent properties at higher scales. Such approaches are equally relevant to the study of eukaryotic and prokaryotic systems (for example from bacterial cell –> biofilms –> microbiome).

Maximising mechanistic insights from data through modelling, curation, sharing, training, informatics and better data visualisation. Recent step changes in studying the single cell have raised the critical need to bring together and learn from data outputs from the above priorities, to properly understand heterogeneity (mechanistic versus noise), cell-type specification and homeostasis and their consequences for humans in health and disease. This will require new paradigms in maths and data integration, able to model dynamic spatial and temporal processes, extending to 'post-genome' data (RNA, lipids and membranes, PTMs, proteome and interactome, metabolites), and integrating curated annotated databases of healthy and diseased states at all levels of scale (molecule -> cell -> tissue -> organ -> individual -> population), to understand causal emergent mechanistic linkages.

Enabling strategies to translate fundamental science discoveries towards the clinic. Extracting maximum value for society requires us to implement technologies, training and opportunities to ensure practical and intellectual reach-through of molecular discovery into clinical utility. To achieve such reach-through, we need both to accelerate the assessment and validation of putative causal and restorative targets through experimental medicine investigations, and to deepen clinical-academic experimental medicine and molecular pathology approaches and early-stage drug discovery. This will help refocus and motivate fundamental researchers in their experimental intent (moving from observation to interrogation and understanding of heterogeneity linked to function) and define the training needs to deliver this (data science and molecular pathology needs in integrated teams).

Building a culture of institute, unit and centre hothouses of technology development, discovery and 'distributable' molecular science and methodologies. To support the above, it is imperative that national investments have an embedded culture of sharing and access provision, to capitalise on their outputs for the national good. This requires stronger integration, both across and beyond these investments, and distribution networks for the tools, technologies and methodologies they develop.

Delivering these priorities will require access to state-of-the-art infrastructure, including: high-resolution imaging; CryoEM and structural studies; metabolomics, proteomics and drug development; capacity development; and the creation of a culture of team science across the boundaries of life science, physical science, engineering, mathematics and medicine.

In addition to the underpinning priorities, the panel identified the following health threats and challenges as being of particular importance:

- **environmental change and health:** anticipatory strategies (such as in the field of AI) are needed to develop and capitalise on existing antipathogens, and to address the impacts of environmental change on pandemic and endemic infectious diseases and of human pathogens crossing boundaries (species and geographic); co-threats arise from non-communicable exposures, which highlights, for instance, the importance of understanding, at the molecular and cellular level, the impact of all pollutants (not limited to air pollution) and toxins on biological processes linked to health and disease
- **healthy ageing:** mechanisms are needed to underpin health-span and ageing and understanding of the molecular and cellular processes involved in immunosenescence and neurodegeneration over the life-course, and how ageing alters molecular and cellular biology and therapeutic response; strategies are needed for 'resetting' and on the importance of interconnected factors of genomic, environmental and social impacts; better understanding of complexity and redundancy is needed to inform clinical trials, along with a move to top-down approaches (for example, in neurodegeneration a move to 'beyond genome' investigations of cause is needed, to ask 'what do neurons need to survive?').

Funding mechanisms

The panel considered options to deliver its priorities, agreeing that longer-term commitments were essential. Members recommended that a seven-plus-seven-year funding cycle would be advantageous for making progress in such new interdisciplinary fields. In addition, having a director providing a clear vision and strategic decision-making, and enabling an open collaborative research culture, was regarded as key. The panel also agreed that there was merit in providing capital equipment schemes for the wider community, such as that provided by the National Institutes of Health (NIH).

Challenge-led approaches

The panel discussed the Janelia Farm challenge- and disease-led model, and how it aligned to the panel's priorities to link 'post-genome' research to phenotype in health and disease. Members agreed that Janelia Farm was an exemplar through its adoption of a 'whatever it takes' approach to bring together the best across chemistry, cell and tissue biology, mathematics and physics (in imaging and modelling, for example) to meet a specified challenge, and by providing access both direct and remote (via on-site hotel and lab accommodation and by distributing reagents, for instance) to the wider community. Members agreed that there is potential merit in a challenge-led approach, with the option of allowing the research community to propose the challenge(s) to attack seen as attractive.

4. Opportunities and implications for the existing portfolio

Comments on the existing portfolio

The panel agreed that the existing unit and centre portfolio had made many significant contributions to the biomedical field through a range of outstanding science programmes. Members considered how the existing portfolio might contribute to the panel's identified priorities, including through transitioning into more 'post-genomic' and mechanistic research, deeper embedding of clinical with fundamental research, and increasing outward-facing visibility and national networking. There was a view that many of the units were perhaps insufficiently focused on linkage to key health issues and insufficiently outward-facing,

Across the portfolio, the panel agreed there was a general opportunity to capitalise and move beyond current focuses (such as genome and chromatin biology) towards 'post-genomic' research (such as lipids, PTMs and metabolites), with an increased emphasis on studying causal mechanistic links. Current investments varied in the degree to which such transitioning was already occurring and, in general, the portfolio of programmes, whilst driving new methods (such as in dynamic biology and supramolecular investigations), would significantly benefit from increased interdisciplinarity, especially to bring in key components of physics and chemistry. Examples considered by the panel included the Centre for Neuropsychiatric Genetics and Genomics (CNNG), which was acknowledged to have had great success in identifying polygenic risk variants but, to date, less success in understanding causal links to psychiatric disorders. This challenge is equally recognised by the centre and by the Protein Phosphorylation and Ubiquitylation Unit (PPU), which was regarded as an example of an investment clearly already playing into 'post-genomic' opportunities. The PPU combines genomic insights from human mutations in the genome (especially in Parkinson's disease) to explore how PTM signalling pathways are impacted, using chemical tools to interrogate these and paving the way for revealing starting points for therapeutic intervention.

The panel agreed that certain of the larger investments, such as the Human Genetics Unit (HGU) and the Toxicology Unit (TOXU), could benefit by strengthening focus, especially to capitalise on 'post-genomic' opportunities. In particular, the panel's priorities could present strong opportunities **for units to capitalise on their research and technology strengths to support the community**. The extent to which the units function as teams rather than groups of individuals was not considered a possible issue.

Turning to priorities at the clinical-academic interface, there were good examples within the portfolio with more translational remits that could also capitalise on the priorities. These examples include the Human Immunology Unit (HIU), which has plans to ramp up research on antibodies and immune response, the Centre for Virus Research (CVR) and the Clinical Research Unit (CRU), with its focus on early detection delivered through genomics and metabolomics. The panel agreed the pressing need for better clinical link-up for the investments that are more focused on discovery research.

There were seen to be opportunities for greater interaction across the portfolio, which may require changes in culture and increased visibility. Although there were examples of such interaction (such as between the CVR and the MRC Uganda Unit), these were limited, with some investments (while recognised as having outstanding individual programmes) perceived to have limited interactions either within or beyond their centre. Members agreed that a very cost-effective and impactful approach to providing regular interconnectivity across the existing portfolio would be through supporting 'brainstorming' retreats, potentially with seed funding to support new collaborations. Early-career researcher and programme and group leaders seconded across sites could also help catalyse interaction. Recent networked institute investments such as the Dementia Research Institute (DRI) potentially also provide templates for this through cross-disciplinary themes and shared post-docs.

In terms of national provision, the panel identified investments that were well-positioned to provide infrastructure and expertise (for example, super-resolution imaging at the HGU and CryoEM and bioinformatics at the CVR). Nonetheless, units especially should be more outward-facing, capitalising on their developed tools and technologies by providing for the national (and international) community. The PPU was an outstanding exemplar, providing tools, reagents and methodologies developed through the unit's programmes.

Across the portfolio, as with the field in general, there were seen to be opportunities for a more 'team science' approach.

Molecular and Cell Domain Panel (all members attended in person)

- **Chair: Professor Doreen Cantrell** (University of Dundee)
- Professor Anne Ridley (University of Bristol)
- Professor David Westhead (University of Leeds)
- Professor Erica Ollmann Saphire (Scripps Research)
- Professor Francis Barr (University of Oxford)
- Professor Giovanna Mallucci (University of Cambridge)
- Professor Jodi Nunnari (University of California, Davis)
- Professor Matthias Hentze (European Molecular Biology Laboratory)
- Professor Mike Dustin (University of Oxford)
- Professor Mike Malim (King's College London)
- Professor Paul Williams (University of Nottingham)
- Professor Peter Parker (King's College London)
- Professor Rob Bristow (University of Manchester)
- Professor Sheena Radford (University of Leeds)
- Dr Trevor Howe (Janssen)

Annex 3: Physiological Systems Domain Panel report

This report provides a high-level view of research needs and opportunities over the next decade within the Physiological Systems Domain of the MRC Unit and Centre Portfolio Review. Informed by existing MRC and other funder strategies and considering national and global health perspectives, the review aimed to identify where unit, centre or equivalent investment could transformationally contribute to UK leadership and to consider, if merited, reshaping the existing unit and centre portfolio to better respond to or add value to this agenda. Recommendations were provided by an independent panel of leading UK and international experts across the domain (see Annex 1).

Executive summary

The panel recognised the need for continuing a mechanism for sustained long-term funding in areas of high scientific need and for MRC to continue to support discovery science and its translation.

The genetic revolution has resulted in unprecedented knowledge regarding gene function, although this increased knowledge has mostly failed to translate into effective therapies to date, often due to lack of understanding of the function associated with these gene products. Physiology offers a means to interrogate function at different orders of magnitude, from cellular processes through to whole organisms, and to thereby identify the level at which diseases emerge and are most amendable to intervention. This will require interrogation and integration of rich data sources, including and beyond genetics, across physical scales and time, drawing on and promoting technological and methodological advances. To identify the most impactful intervention approaches, a more explicit consideration of environmental and social drivers of disease is also required.

Fostering interdisciplinary research (including physical, mathematical, environmental and social sciences) and enhancing data-scientist capacity were identified as key opportunities to engender improved understanding of human biology and disease. An outstanding challenge remains building new frameworks to work collaboratively with the private sector and to engage more with venture capitalists at an early stage in research.

This review identified the following as priority areas of opportunity and need where investment would be transformational in providing or maintaining UK leadership:

- **physiology and biochemistry of cells and tissues,** including understanding of how a heterogeneity of cell types collectively contribute to tissue function
- **microbiome and health,** where there is a need for a national capability to develop baseline data and standards
- **healthy ageing,** with a focus on the mechanistic basis of ageing and options for intervention
- **climate change and health,** in recognition of both the primary and the secondary impacts such change may have
- **mental health,** which was recognised as a pressing and growing health challenge.

The proposed investments would be large multidisciplinary investments connecting existing resources and generating capacity in skilled scientists, to improve UK health and health globally. In addition, and underpinning all its identified priority areas, the panel supported the need for increased capacity and capability development in physiology and data sciences.

Finally, the panel noted the desirability of enhanced working across units and centres where there were common themes.

1. Developing the list of key areas of opportunity and need

The following provides a summary of the key outputs resulting from the panel discussions covering the dimensions set out in the review's terms of reference: scientific development, national research capability (for example, platforms and resources) and accelerated impact.

A. Threats and challenges to sustaining and improving health

Extending a healthy lifespan

Maintenance of healthy ageing, including supporting an ageing population, was identified as a key driver for several threats to human health:

- **multimorbidity:** increasingly people are living with more than one medical condition, and some conditions are drivers of development of alternative conditions (for example, an increased risk of developing type II diabetes or cancer is correlated with obesity); much current therapeutic assessment excludes people with multimorbid conditions and the panel recognised the need for novel interventions in both people with multimorbidities and the elderly, including innovative use of population data on polypharmacy and 'real-world evidence' studies; it was recognised that greater interaction between funding bodies would be required to fully address this issue, particularly between MRC and NIHR
- **frailty and immobility:** despite leading to the largest increase in disability-adjusted life years (DALYs), frailty and immobility remain relatively underfunded in comparison with other areas, such as cancer; an ageing population is predicted to see an increase in immobility and frailty, the impact of which is often greater with social isolation in the elderly; this area would benefit from closer integration with engineering solutions.

The body-mind interaction

A need was identified to explore further the link between physiology and neurological and mental health. This includes broader issues such as:

- **the microbiome** and its influence on human physiology, disease and therapies
- **inflammation** and the link between inflammatory processes and mental health, including the link between depression and inflammation and psychosis and autoimmune diseases
- **chronic pain** and the perception of pain more generally
- **chronobiology,** which underpins many responses from vaccine responsiveness to insulin secretion.

Addressing this need will require overcoming sometimes entrenched perspectives arising from training that classify people by disease and/or system (for example, neurologist v immunologist when we need to think anew in terms of neuroimmunology).

Cancer

The UK has lower survival rates for many cancer types than other higher-income countries and the panel agreed a requirement for early detection, prevention and further research into the tumour microenvironment.

Mental health and behaviour

A key challenge, both globally and nationally, was to drive change in human behaviour, including altering habit formation and enhancing health education. Psychiatric disorders and addiction remain national issues which continue to affect health. The panel highlighted social isolation and access to blue and green spaces as issues affecting national mental health.

Anthropogenic changes

These were identified as key drivers for several threats to human health both nationally and globally, and include:

- **climate and environmental change:** increased occurrence of extreme variations and unpredictability of weather patterns leading to short term as well as longer-lasting effects (such as flooding, coastal inundation, drought and desertification) and linked to rising global temperatures were considered a major challenge to health; sustained changes in the global and ecological environment would impact land use, compromise global food and water security, and lead to mass migration and a shift in the geographical distribution of infectious and non-infectious diseases; it was recognised that greater interaction would be needed between climate change and biomedical research domains to fully address this issue
- **pollution:** in increasingly urbanised areas, the role of pollutants (air, water, nanoparticulate matter) was considered a significant threat to human health; consideration of environmental interplay and barrier (gut and lung) physiology to manage the complex interactions between the environment and the human body would be required to address this issue
- **infectious disease epidemics and AMR:** in an increasingly interconnected world and highlighted by the COVID-19 outbreak (declared a World Health Organisation Public Health Emergency of International Concern), the emergence of infectious disease epidemics was considered a significant threat to human health; consideration of complex health systems, including cross-cutting factors such as the environment and social factors, would be needed; in addition, AMR and pandemic preparedness and response were viewed as key challenges to global health.

To address these issues, the panel recommended that there should be a greater emphasis on **prevention**, including taking a **more holistic approach,** to take greater account of the environmental and socio-economic contributions to health and disease biomedical research. **Enhanced interactions** across multiple sectors are required to ensure that researcher-driven findings are translatable at scale and at cost, ensuring that new therapies and diagnostics are available where they are most needed in a manner which fits the resource setting.

B. Research innovations and opportunities to develop fundamental new insights and/or address identified health challenges

Redefining disease focus

An opportunity was identified around refocusing and redefining diseases, removing specific focal points (such as ischaemic heart disease) and investigating disease processes that are common to multiple diseases (for example, fibrosis and inflammation). However, responses may be different depending on the organ affected and there are clear needs to integrate such actions with precision-medicine approaches.

Physiology

Although the increasing availability of genetic data has led to increased understanding of monogenic diseases, most issues affecting human health incorporate an element of genetic risk, tissue or organ performance, coupled with environmental exposure. There is an opportunity to integrate whole-genome data with exposome data to generate richer datasets. However, it was recognised that an enhanced understanding of physiology has now become the rate-limiting step in understanding the impact of genetic data.

Integrating across scale and time

Measuring at different sales (from single cells in their tissue niche, using 'omic technologies, to individuals in their natural environment, using wearable devices) and across multiple timepoints was identified as presenting key opportunities. These include at the tissue level, where it is now recognised that there is significant spatial and temporal heterogeneity with real medical implications, and in integrating metabolism of single cells and tissues. In the brain, temporal change ranges from the speed of neuronal activity, which makes transcriptional change appear static, all the way through to studies of brain development, which can run over a lifetime.

Integrating across scale and time will require access to existing state-of-the-art equipment and the staff to support it, the development of new technologies able to interrogate across scales and capture flux, and new mathematical statistical tools able to address the very different temporal dynamics. In developing new technologies, consideration should be given to frugal options, to enable their deployment in resource-limited environments.

Collectively, a consideration of disease across scale and time should enable a better understanding of the level at which diseases emerge and may be best addressed.

Integrating across disciplines

Advances in medical technologies are often driven by methodologies discovered in alternative fields. For example, the increased resolution that has led to magnetic resonance imaging (MRI) becoming invaluable to the neuroscience and psychology fields had its beginnings in physical chemistry. Bringing together physical sciences, biomedical researchers and clinicians in an institute for physical sciences and medicine would provide the opportunity to both develop new techniques and accelerate clinical applications for such techniques. Showcasing events and supportive funding schemes were recommended as means to make such productive exchange more likely and rapid, as such work was regarded as falling in the gap between existing funder (EPSRC, MRC) schemes.

Cohorts and data

The UK has good strengths in longitudinal cohorts, yet there is a need for innovation to drive the integration of differing datasets. There are currently multiple places for data interrogation, rather than a centralised national resource which could support both the investigation of data in a similar manner across multiple datasets and the integration of different data types, enabling modelling. With modelling of data (and subsequent iterative validation of the models produced), using AI and machine learning to configure algorithms and actionable pathway analyses remains an opportunity to develop new insights into disease processes.

Seizing the data and modelling opportunity will require quality measures to indicate the value of existing datasets and will critically need sufficient capacity and training in data and mathematical science, and support for methodology development.

It was noted that there still remains considerable need for methodological development in the integrative analysis of multiple datasets from diverse sources.

Examination of outlying datapoints

Within clinical studies, individuals who are identified as extreme outliers (for example, those individuals who are particularly resistant to a disease) are normally excluded from current analyses. These individuals can provide a tremendous amount of information on underlying common disease processes through extreme mutational analyses, and the identification of genes associated with resilience could accelerate the therapeutic discovery process. Linking with mental health, individuals who do not develop mental health issues despite being exposed to a range of high-risk factors could similarly provide direction for enhanced cognitive therapies.

C. Accelerating impact and infrastructure

Interdisciplinarity and cross-sectoral mechanisms

Promoting interdisciplinary research and establishing cross-sectoral funding mechanisms were considered essential to addressing major health challenges and achieving a step change in the capability of UK population health science. The establishment of UKRI was viewed as a significant transformation of the UK science landscape, facilitating closer connections between diverse research disciplines which have traditionally operated in isolation, although it was noted that there are few cross-council centres within the current MRC portfolio of large investments.

Interdisciplinary research approaches outside the biomedical sector would enable the integration of new technologies, methods and expertise from a wide range of fields including computer science, engineering, social sciences, economics and environmental science. It was recognised that to develop a trans- and multidisciplinary research workforce would require re-evaluation of the career and training frameworks for undergraduate and postgraduate education that permit cross-disciplinary movement and sustainable career pathways.

In addition, approaches are needed that promote closer working between academic, health (NHS) and private (industry) sectors together with stronger linkage of research with the management of health. In relation to the private sector, there is a need to position investments and ambitions to attract company partnerships.

In relation to the public sector, joint MRC-NIHR centres with a focus on experimental medicine were proposed to use pathway analysis to redefine disease areas. Broadening research from current silos of excellence to wider pathways could have a huge impact in a wide range of areas, harnessing our understanding of disease pathways and applying this to disease stratification and personalised medicine. It was recognised that there are centres within the population health domain which may benefit from closer integration with those centres operating on a more mechanistic level. Such pooling of resources is predicted to increase understanding of disease and physiological systems.

Data and data analysis

A centralised data analysis portal with appropriate data-handling environments was proposed in order to analyse data in a uniform manner. This was envisaged to have a strong training component, in order to provide outreach services to current large investments and enhance AI and machine learning capabilities in the UK. Enhancing data visibility was seen to be key to improved data reproducibility.

Engagement with citizens

Current clinical trials often do not address the diversity agenda and different therapies can differ significantly in their effects on minorities and should encompass the spectrum of social status, age, gender and ethnicity. Public engagement and enhanced interaction with the public across UKRI would be beneficial and could lead to citizen scientists, who through co-development may be encouraged to interact and provide phenotypic data through the advancement of new technologies.

Changing the culture of translational research

Research conducted by academic researchers in UK universities can be successfully translated into small and medium-sized enterprises (SMEs) through institution-led funding delivered by the MRC Developmental Pathway Funding Scheme. Subsequent successful academic and industry endeavours can further be stimulated by funding delivered through IUK; however, these funding streams struggle to align with other translational funding schemes. To enhance translational success, it would be beneficial to incorporate concepts of agility, continuous planning and 'fail fast, fail cheap', and different reward systems from supported companies. Incorporating clinicians into translational research is critical, to help identify gaps in the market and ensure affordability of final product.

Training and careers

An improved strategy for training, careers and capacity-building is needed, particularly across physiology as a discipline, together with data and computer science to ensure the next generation of scientists are adequately equipped to generate and implement new methodological approaches. We should train for interdisciplinarity, to prevent siloed mentalities and to allow scientists to work across disciplines; similarly, clinicians and scientists should be trained together to allow for dynamic exchange and enhance the translational pathway.

2. Longlist of key areas of opportunity and need

Drawing on perspectives from across the three the three themes (A, B and C above), the panel developed and agreed a longlist of areas of opportunity and need in the physiological systems domain over the next decade (see Table 1)[2] .

Table 1: Longlist of key areas of opportunity and need identified by the panel

Area of opportunity or need	Comments
Physiology	■ Recognised need for increased capacity in physiology ■ Lack understanding of what genes do; need to understand how a heterogeneity of cells work in a tissue: cellular function in a tissue context, right down to molecular function and consideration of tissue and organismal biology ■ Dynamic component as well; mathematically challenging and experimentally hard ■ Opportunity of partnership with BBSRC
Data	■ Not just data science but also modelling ■ Critical to get EPSRC buy-in as it is the council that mathematicians really engage with ■ Opportunity for interaction with pharma (such as target validation) ■ Methodology not well supported in response mode or by career paths, so could argue for strategic investment
Chronobiology	■ Important area that could be a unique aspect of the MRC portfolio ■ Affects a wide range of physiological systems with impacts, for instance, on vaccines, drug action and metabolism, and stress ■ Consideration of micro- and macro-scale time models, helping to integrate cellular and physiological processes ■ Timely, as Academy of Medical Sciences is organising a workshop in this area
Sensors and integration of physical sciences and engineering into medicine	■ Interrogation of whole-body physiology, imaging, wearables (long-timescale dynamics) and implantables (shorter-term physiology) ■ Demonstrating real-world value of medicine to patients and physicians by measuring patient-centric outcomes (c.f. fatigue and tiredness) ■ Risk and opportunity of private sector doing this more quickly; important role for MRC supporting interaction with companies, and for rigorous assessment of new technologies ■ True integration of physical sciences, biomedical scientists, health economists and clinicians will feed the translational pipeline ■ Need for frugal solutions for low- and middle-income countries (LMICs)
Outliers	■ Currently a focus on people with risk alleles, while those who do not develop disease are ignored ■ Addresses common disease pathways ■ Useful resource for drug discovery and common disease pathways
Experimental medicine	■ Experimental medicine done well in the UK, but there are rather disparate approaches across the country; a diminishing cadre of exponents ■ There may be opportunities for centres in advanced therapies, with wider experimental medicine needs benefiting from more distributed models ■ Could be an opportunity to engage with other funders (such as NIHR) to provide training in this important area and increase underpinning mechanistic understanding
The microbiome and health	■ Interactions with a wide range of diseases (such as obesity) ■ Could use omic technologies in the area of the gut-microbiome interface and involve immunology
Healthy ageing	■ Probably the single most important health challenge ■ Brings in a wide range of other areas (including cancer, regenerative medicine and wearable devices)
Multimorbidity	■ Dominant theme but much activity already and with further opportunities for engagement with other funders (such as Cancer Research UK, the British Heart Foundation and NIHR) to tackle this important topic
Cancer and immunology	■ Given the scale of existing activity, it is difficult to find an area where a distinctive contribution could be made; possible opportunity in immunology in the context of tissues (cancer, homeostasis, regeneration) ■ Challenge of siloed perspective of immunologists

2 The list was not restricted by whether the areas would or would not benefit from unit, centre or equivalent investment.

Mental health	■ A key driver for prevention which is relatively poorly understood ■ Clear involvements in addiction, prevention, health education and interplays with mental health ■ Could be a unique aspect for MRC ■ UK Prevention Research Partnership (PRP) addresses some aspects, but more mechanistic research is needed ■ Wellcome may invest heavily in this area
Climate change and global health	■ Enhancing partnerships between south and north and transferring expertise and protocols from LMICs to the UK ■ Ensuring diagnostics and new therapies are suitable for resource-limited environments (needs involvement of health economists)

3. Prioritised areas of opportunity and need

The panel further prioritised those areas in Table 1 that would most benefit from unit, centre or equivalent investment, including consideration of the form that the investment might take.

Physiology and biochemistry of cell and tissue biology

The panel agreed a need to invest in the broadest sense in physiology and biochemistry, with a key component being training in these disciplines. With the wealth of information now available from genetic studies, the bottleneck in increased understanding is comprehending the cellular function within a wider tissue component. The panel additionally recommended consideration of how the heterogeneity of cells function within specific tissues, organs and systems. The panel considered there was large investment in technology in these areas but there remains a lack of physiological experts to make sense of this data. Training should involve reskilling researchers with tools to examine cellular, tissue and organism physiology and could be delivered through a partnership between MRC and BBSRC. The panel identified that there are physical (structural and biomechanical) and dynamic components to physiological systems which need to be accounted for. The dynamic aspect is both mathematically challenging and experimentally difficult to address, yet the opportunity it presents for increased knowledge across scales was deemed to be important.

Microbiome and health

The panel agreed that the future impact of enhanced understanding of the microbiome and the effect on health was substantial. There is some limited MRC activity already within this area, but the panel suggested there was a need for a microbiome unit or centre providing a national platform capability; this could provide shared equipment, baseline data and supporting standards, with a specific agenda (for example, on mental health or obesity). The panel agreed that such investment would require a significant training component to help build UK capacity within this field, given the field's potential impact on, for instance, AMR, and to encourage researchers to work on wider public health dimensions.

Healthy ageing

A reduction in the negative effects of ageing will have an impact on a wide range of diseases and dramatically improve human health. We are now in a position to understand the cellular mechanisms which drive ageing and which could provide targets for therapeutic intervention. The panel suggested a directed unit in this area to dynamically interact with other disease paradigms and systems supported by other large investments. Key partners in this venture could be BBSRC and NIHR and this unit could investigate immunosenescence, basic biology of lifespan and pathophysiology of ageing. There could be an opportunity to interact with the UK Regenerative Medicine Platform (UKRMP) to potentially reverse pathological processes during ageing, either through activation of endogenous systems (c.f. repair) or through the introduction of exogenous factors (c.f. cell therapies).

Climate change and health

The panel supported expanding the breath and expertise of existing investments to establish a strong initiative centred on environmental change (for example, climate change) and its impact on health, especially in LMICs. This area cross-links to infections, health services and resilience.

Mental health

Mental health was viewed as a strategically important area, particularly in adolescents and the young in an ever-changing world of new technologies and modes of social interaction. A focus on prevention of mental health problems was considered essential, together with greater understanding of the common environmental and behavioural risk factors and exposures including the roles of inequality and poverty (the biggest predictor of poor mental health). Mental health was noted as an underrepresented area of the MRC portfolio and a need was identified to re-evaluate the classical framework of prioritising physical health over mental health. Better understanding was also needed on the interaction between the body-brain interface and mental health in the context of multimorbidities and a move towards a multicomponent view of health.

4. Opportunities and implications for the existing portfolio

Comments on the existing portfolio

The panel agreed that the existing portfolio had made significant contributions to the field and was convinced that there remains a need for long-term, stable funding, beyond the five-year grant cycle, to support fundamental discovery that presents translational opportunities. However, requirements that existing investments focus on static objectives with minimal divergence were viewed as a constraint of the current model, contributing to a lack of agility to adapt and respond to new technologies and insights. Members recommended that a reduction in bureaucratic burdens on leadership might assist in this regard. It was also noted that there was a paucity of visible interaction within the portfolio and of shared units and centres both across UKRI and among cross-funders (such as NIHR and charities).

MRC has appreciable existing centre and unit investments in physiological systems, which could provide valuable contributions to the panel's identified priorities; however, gaps were identified in healthy ageing and the microbiome. In addition, it was agreed that the portfolio could benefit from increased consideration of environmental and social drivers and solutions.

Regarding the area of cellular heterogeneity of tissues, both the MRC Centre for Regenerative Medicine and the Wellcome-MRC Cambridge Stem Cell Institute were seen to have complementary contributions to make, the former providing tissue context and translational opportunities and the latter being recognised as leaders in integrating transcriptomics and other omics into cellular behaviour.

Physiological Systems Domain Panel

- **Chair: Professor Jonathan Weber** (Imperial College London)
- Professor Ceri Davies (Takeda Pharmaceuticals) *Apologies*
- Professor David Scadden (Harvard University)
- Professor Derek Jones (Cardiff University)
- Professor Fiona Powrie (University of Oxford)
- Professor Dame Frances Ashcroft (University of Oxford)
- Professor Ian Hall (University of Nottingham)
- Professor Jane Norman (University of Bristol)
- Professor Jimmy Moore (Imperial College London)
- Professor John Terry (University of Birmingham)
- Professor Kenneth Boheler (Johns Hopkins University)
- Professor Paul Stewart (University of Leeds) *Apologies for day 1*
- Dr Regina Fritsche Danielson (AstraZeneca)
- Professor Sarah-Jayne Blakemore (University of Cambridge)
- Professor Valerie O'Donnell (Cardiff University)

Annex 4: Population and Public Health Domain Panel report

This report provides a high-level view of research needs and opportunities over the next decade within the Population and Public Health Domain of the MRC Unit and Centre Portfolio Review. Informed by existing MRC and other funder strategies and considering national and global health perspectives, the review aimed to identify where unit, centre or equivalent investment could transformationally contribute to UK leadership and to consider, if merited, reshaping the existing unit and centre portfolio, to better respond to or add value to this agenda. Recommendations were provided by an independent panel of leading UK and international experts across the domain (see Annex 1).

Executive summary

Today there are rapidly emerging and developing health challenges consequent upon massive global changes (such as climate change, urbanisation and population ageing) which are having profound effects on human health, health systems and sustainability. These coincide with an exponential growth in the breadth and depth of data being collected on the health, welfare and behaviour of populations. This provides population health science with an unprecedented opportunity to identify and test interventions aimed at protecting and improving the health of the population in the UK and globally.

Until recently, population health science has not had the data or the methodologies to adequately account for the full breadth of factors that impact on population health. However, with the right investments and training we are poised to be able to develop integrated approaches to understanding and then intervening in the drivers of population health, from the molecular through to the environmental, political and social. This will require a new approach to fostering interdisciplinary research spanning diverse sectors and embedding data scientists alongside biomedical researchers and public health experts within research structures to engender new ideas and methodological approaches beyond those currently employed.

Over the last decade the scale and depth of digital health and related data in the UK has expanded exponentially. This includes the wealth of nationally collated NHS routine healthcare datasets and large-scale national investments to establish population-based collections such as UK Biobank, Genomics England Limited (GEL) and the Accelerating Detection of Disease programme (ADD). Ensuring that these data collections are extended to include relevant behavioural, environmental and socio-demographic data will result in a step change in how population data at scale can be used to understand and improve human health. An outstanding challenge remains the building of new frameworks to work collaboratively with the private sector which reflect that it is the NHS and the public research community that owns much of the relevant data, but that the private sector has a concentration of expertise and innovation in developing state-of-the-art 'big data' analytic approaches.

This review identified the creation of an Institute for Population Health Intervention and Improvement as the overarching priority. This would be a large challenge-led, multidisciplinary investment harnessing the revolution in data on individuals' health and behaviour, the health sector and the environment. Its brief would be to develop and test approaches to sustain and improve population health (both mental and physical) at a national and global level, and to reduce persistent geographic and socio-economic health inequalities.

In addition, the panel identified the need for separate and specific funding initiatives on infectious diseases with pandemic potential, mental health and global environmental change, and supported the need for increased capacity and capability development in data science.

1. Developing the list of key areas of opportunity and need

The following provides a summary of the key outputs from the panel discussions covering the dimensions set out in the review's terms of reference: scientific development, national research capability (such as platforms and resources) and accelerated impact.

A. Threats and challenges to sustaining and improving health

Global health threats

Anthropogenic changes were identified as key drivers for several threats to human health both nationally and globally, and included:

- **climate and environmental change:** an increased occurrence of extreme variations and unpredictability of weather patterns leading to short-term as well as longer-lasting effects (such as flooding, coastal inundation, drought and desertification) and linked to rising global temperatures were considered a major challenge to health; sustained changes in the global and ecological environment would impact land use, compromise global food and water security and lead to mass migration; this is likely to have a huge negative impact on health infrastructures in resource-poor settings and result in a shift in the geographical distribution of infectious diseases and mental health disorders (for instance, via disruption to human networks, and mass migration); it was recognised that substantially greater interdisciplinary interactions would be needed between climate change and biomedical research domains to fully address these issues
- **infectious disease epidemics and AMR:** in an increasingly interconnected world and highlighted by the 2019 novel coronavirus outbreak (declared a World Health Organisation Public Health Emergency of International Concern), the emergence of infectious disease epidemics was considered a significant threat to human health; developing a systems-level understanding of the interaction of environmental and socially driven changes in how animals and humans interact will be needed; in addition, AMR and pandemic preparedness and response were viewed as key challenges to global health
- **demographic dynamics:** the ageing of populations was recognised as a strong driver of later-life non-communicable diseases (NCDs) and conditions (such as dementia, heart failure and physical frailty) and later-life communicable diseases and multimorbidities, leading to increased demands on the healthcare sector; very recently it has also become clear that we can no longer assume that life expectancy and health in the UK and other higher-income countries will continue to improve, with evidence of stalling life expectancy overall and increasing health inequalities (social and geographical) becoming more entrenched; from a global health perspective, the panel also identified urbanisation and its consequences as important challenges, including the increasing burden of NCDs in LMICs.

Developing an integrated systems approach to intervention and prevention

A need was identified to expand beyond the biomedical domain and integrate biological, behavioural, social, political and environmental (physical) factors that govern and influence our health. Importantly, this should encompass both mental and physical elements of health.

Inequalities

Social and geographical inequalities were viewed as a challenge across the population and public health domain. Approaches are needed to reduce health inequalities. [This has been further underlined since the panel meeting by the publication of the Marmot 2020 report.] Several groups excluded from the vast majority of research studies (as well as from society more generally) need to be prioritised, including refugees, the homeless, disabled individuals and drug users, mental health often being a particular issue in these groups.

Shift towards intervention and implementation

Population health research needs to move further towards addressing how to turn insights in determinants of population health into effective interventions that are implemented at sufficient scale to have population impact. This will require working with the public, local authorities, the NHS and others to formulate priority issues for research. Greater innovation was required around approaches for engagement with the public to better understand health-related behaviours and motivations at the individual level.

Engagement with the private sector

A key future challenge is improving the interface between academia and the private sector. This requires the development of new frameworks for working collaboratively with industry, including companies with extensive expertise in, and resources for, exploiting the huge amount of digitised data on individuals. Some of the big technology companies have large volumes of multidimensional health-related data (on fitness, behaviour and lifestyle, for example) with the potential to enhance existing population datasets. From the other side, it is the NHS that controls data on healthcare

and health sector use. Significant barriers remain in relation to data access and working with private sector companies, with many commercial products and services proprietary and substantial public distrust around healthcare providers partnering with private entities.

Destructive marketing

The substantial promotion of products and services by large companies with local, national and global reach was identified as a major challenge to human health. This included the promotion of online gambling through popular outlets such as sport; high in fat, salt or sugar (HFSS) foods and drinks; and alcohol, tobacco and nicotine products. Destructive marketing and, more recently, large-scale online targeted advertising through social media had the potential to modify behaviour, cultural beliefs and practices and undermine responsible public health messaging. There may be opportunities to learn from these approaches for public good.

To address these rapidly changing threats and challenges, the panel agreed that we need improved methodologies to study their drivers along with **far more agile, adaptive and rapidly responsive research structures.** An additional challenge noted was the issue of engaging across sectors and industry and being able to capture the necessary data science and engineering expertise within the public sector, which tends not to be able to offer the same salaries as the private sector.

B. Research innovations and opportunities to develop fundamental new insights and/or address identified health challenges

Data at scale in the whole population

An opportunity was identified around the utilisation of data at scale in the whole population (including those often excluded from research studies). This would include data covering NHS healthcare interactions, much of which is now collated at the national level (for example by NHS Digital and other bodies), a multitude of human interactions in the social and natural environment (for example using mobile apps, social media, wearables and smart home devices), together with the recent exponential rise in omics data. Greater understanding of the type of information needed to meet specific scientific challenges would be required. Analysis of data at scale would need sufficient capacity and training in data science together with quality measures of the value of existing datasets.

New technology for partnership

Advances in technology can be exploited in downstream health informatics to better inform healthcare planning delivery. Healthcare provision and telemedicine provide a rich data resource to better understand health and to intervene. This applies to the Global South as well as higher-income settings such as the UK. Babylon Health in Rwanda, where the main stream is digital, provides an example of the use of real-time health system data being rolled out at scale in a low-resource setting. However, there remains a need for equitable assessment of the role of private healthcare providers adopting this approach. This opportunity could extend beyond telemedicine and centre on remote delivery and self-management of health, utilising a combination of technology and behavioural science. Robust data curation and governance would be essential to balance the needs of accessibility with security. One approach would be for participants to become more active agents or partners in generating and using data and for this to be the default relationship between researchers and the public. It was noted that this is the default assumption of most online platforms that collect information about people through, for example, wearable physical activity monitors.

Behavioural change

Our current understanding of behavioural change through a systems approach is inadequate. Better measures of behaviour and systems for collection and analysis of real-time data are needed to provide a more complete understanding of how to implement policies aimed at improving population health. The public acceptability of policy recommendations is an important factor in influencing behavioural change. However, the main problem is successful engagement and interaction with people.

Cross-sectoral and cross-disciplinary working

The creation of UKRI was recognised as an opportunity for a more radical reconfiguration of research innovation through greater multidisciplinary and cross-sectoral working with diverse fields such as engineering, economics, architecture and data science. A need was identified for evidence synthesis across disciplines that is both scalable and rapid (automated), involving conceptualising new approaches such as the use of AI. New frameworks would be needed to promote the establishment of research teams covering biomedical, social and environmental science that better connect to policy and interventions. In particular, biostatisticians and data scientists need to be more closely integrated and embedded throughout current investments.

Implementation and intervention a priority

The approach to population science has remained largely static for decades, which is reflected in current investments and resources. Too much emphasis has been placed on describing the problem with insufficient research on implementation and intervention. A gap in the portfolio was identified in the science of translating knowledge into impactful interventions and policies, with a broader view

needed on interventions, including but extending beyond medical treatments. New methodologies, enabling the integration of complex systems approaches, are needed for devising and testing interventions at scale and speed. Implementation science has emerged as a new field that offers new frameworks and methods to accelerate delivery of effective interventions identified in earlier phases of research to populations that need them. It was agreed that a new approach and coherent strategy were required to enable researchers to obtain funding for such methods' development.

C. Accelerating impact and infrastructure

Interdisciplinarity and cross-sectoral mechanisms

Promoting interdisciplinary research and establishing cross-sectoral funding mechanisms were considered essential to addressing major societal challenges and achieving a step change in the capability of UK population health science. While this has often been called for, it takes on a new urgency if we are to effectively exploit the huge increase in data available covering all aspects of individuals, society and the environment in order to improve human health.

The establishment of UKRI was viewed as a significant potential transformation of the UK science landscape, facilitating closer connections between diverse research disciplines which have traditionally operated in isolation. Interdisciplinary research approaches outside the biomedical sector would enable the integration of new technologies, methods and expertise from a wide range of fields including computer science, engineering, social sciences, economics and environmental science. It was recognised that to develop a trans- or multidisciplinary research workforce would require re-evaluation of the career and training frameworks for undergraduate and postgraduate education that permit cross-disciplinary movement and sustainable career pathways.

Strengthen translation and implementation science investments

Translation was considered more than a 'bench-to-bedside' process and should span prevention, delaying ill health and influencing health-related behaviour. Currently, too much weight is placed on increasing knowledge to drive translation and it was agreed that investments should be shaped from an early stage with the purpose of delivering impact on specific challenges, a philosophy that should be fostered in long-term and national focal-point investments. Efforts are needed to strengthen implementation science within the portfolio and to embed research uptake and strategies for impact, ensuring that these are co-produced at an early stage with broad engagement from all relevant stakeholders (including patients, the public and policymakers). There should be much greater emphasis on health intervention studies, including establishing links with existing investments to deliver rapidly and at scale.

Structural agility in investment

A key need was identified for future investments to have greater structural agility, with the capability for science programmes, people, skills and translational ambitions to rapidly adapt to changing scientific needs. A shift towards focusing on challenge-led rather than knowledge-driven programmes would be valuable. Enabling a 'start-up model' to be adopted with its 'fail fast, fail cheap' approach, with continuous re-evaluation of research strategy, would promote such agility. The broader portfolio could consist of a combination of a larger national investment (such as an Institute for Population Health Intervention and Improvement) and smaller, more agile, challenge-focused investments. Financial and budgetary authority would need to be devolved to support these new agile structures with built-in horizon-scanning objectives and associated budget. One approach discussed was a more fluid model or framework where researchers could move between host university and core-funded unit positions, to better meet evolving unit goals.

Data assets

The UK has several strong national investments such as UK Biobank, HDR UK, GEL and ADD. However, work is needed to better connect and maximise access to these and other resources, and to ensure that the information collected on individuals extends beyond the strictly biomedical to include behavioural and socio-demographic factors. Existing MRC portfolio cohort resources were established primarily to provide insights into determinants of disease and have not in general been sufficiently geared towards addressing issues of translation and health improvement. The panel saw an opportunity to make better use of the existing MRC investment by further encouraging cross-working across cohorts to make best use of data science, devices and innovations in social and behavioural science. To optimise the utilisation of data across population science and beyond, open access to data is essential as is more widely the case in some other areas of biomedical research. To provide open access, challenges including behavioural (such as academic territorialism) and technological barriers need to be overcome. Support should be provided for agile approaches and methodologies to take advantage of new data and opportunities. Cohorts need to be linked to whole-

population data assets to contextualise and embrace wider national and international data. It will be important to enrich existing data assets, especially with respect to currently excluded and underrepresented groups. New devices (such as Apple watches) were recognised as a rich source of data often superior to academic research data, highlighting the need for industry partnerships. This data could provide valuable insight into human behaviours at the individual and population level and across the healthcare system.

Training and careers

An improved strategy for training, careers and capacity-building is needed, particularly across data and computer sciences, to ensure the next generation of scientists are adequately equipped to generate and implement new methodological approaches. This will require career and training structures that permit the integration of data scientists within research investments, while also enabling them to operate within their own framework and peer group. Building up capacity in implementation science is also a priority.

2. Longlist of key areas of opportunity and need

Drawing on perspectives from across the three themes (A, B and C above), the panel developed and agreed a longlist of areas of opportunity and need in the population and public health domain over the next decade (see Table 1)[3].

Table 1: Longlist of key areas of opportunity and need identified by the panel

Area of opportunity or need	Comments
Infections (epidemic or pandemic disease)	■ Systems approach needed, integrating biological, social, environmental factors ■ Adoption of a One Health approach (including human, animal, environmental health) ■ Improved modelling (such as AI, with better global information flows) and, importantly, moving beyond modelling to intervention
Improving data and information analytic capacity	■ Enhancing the weight of the portfolio in methodological research and providing additional funding for method development ■ Building up human capacity in data science (integrating biological and systems insights with maths, data engineering, stats skills) ■ Retaining capacity despite the large pull to the private sector (for example due to more attractive salaries and research environments) ■ Developing new robust models for working with private sector data companies ■ Development of methods for testing interventions at scale and speed
Broadening whole-population data	■ Maximising the value of existing large data-collection initiatives by enriching them with data on behaviours, socio-demographics and so on ■ Robust data curation and governance, balancing accessibility and security with acceptability ■ Participants as partners in research: reflexive relationship between scientists and public (through mobile apps, for instance)
Integrated approaches to maintaining and improving population and public health	■ Focus on challenge-led v. knowledge-driven programmes (embed research uptake and co-produce with all stakeholders from the start) ■ Responsive and agile approach required to adapt to new technologies and insights ■ Integration of multidimensional data at scale to address real-world variation in health across geography, social groups, ethnicities, age ■ Promotion of an open-science agenda; overcome behavioural and technological barriers to data access ■ Interdisciplinarity and cross-sectoral mechanisms: linking across academia, NHS, industry and across disease silos and research disciplines ■ Strengthening implementation science utilising new frameworks and methods to accelerate delivery of effective interventions ■ Driving information synthesis and research uptake and strategies for translating information into interventions and impact
Global health	■ Improving data and information analytic capacity in a global health context ■ Accelerated development of digital infrastructure for healthcare and population-based research at scale ■ New approaches to data collection, biological assay, measurement in resource-poor settings (for example, use of AI for triage, suitable portable point-of-care devices) ■ Challenges of and opportunities for working with the private sector, such as mobile network providers, Babylon Health in Rwanda (Babyl)
Environmental change	■ Greater recognition of the effect of the environment on health (such as increased disease susceptibility and severity due to weather extremes) ■ Represents a threat to food systems and disruption to health infrastructure that could lead to mass migration and conflicts within and between countries, with impacts on infectious disease transmission and mental health, for instance ■ Cross-cutting impact that can lead to cumulative disruption to human networks (for example, mental health issues) and infrastructure, including public health programmes
Mental health	■ A key driver of disability and morbidity that is poorly understood ■ Framework of a single-disease model for NCD epidemiology does not apply well and needs revision; the current portfolio is largely disease-specific, which has excluded mental health research ■ Mental health considered important in terms of the multimorbidity agenda, where it is often seen as a follower rather than a leader, and the interaction between mental and physical health
Longer-term influences on health and behaviour over the life-course	■ New framework and methodology required to address the changing influences on health and behaviour in the 21st century ■ Despite the UK having valuable long-term and birth cohorts, the source of future data is unclear (need to establish new cohorts, for example)

3 The list was not restricted by whether the areas would or would not benefit from unique centre or enhanced investment.

3. Prioritised areas of opportunity and need

The panel further prioritised those areas in Table 1 that would most benefit from unit, centre or equivalent investment, including consideration of the form that the investment might take.

Institute for Population Health Intervention and Improvement

A gap was identified in the existing portfolio for an institute or equivalent strategic initiative to improve population health. This would be a new multidisciplinary, methodology-driven investment that would maximise the value of large-scale data collections, with an emphasis on translation of complex preventative and interventional approaches from science conceptual development to impact. It would adopt a challenge-led approach, developed through patient and public engagement, and have a broad focus on improving population health within the UK and globally, including the persistent and pervasive challenge of health inequality. The institute would be a departure from a relatively conservative academic model to one with greater structural agility, enabling a responsive approach to emerging technologies and insights. It could take the form of a physical entity (such as a hub-and-spoke model), a UK-wide institute with a small coordinating HQ such as HDR UK, or networks of consortiums to bring together the necessary expertise and human resource. The institute could help drive investment that capitalises on HDR UK infrastructure and capability.

Infections

The panel agreed that greater traction could be gained in this area through a cross-council initiative consisting of specific funding calls. A mechanism would be needed to strategically link expertise across disciplines, including social and environmental elements which play an important role in disease transmission (for example, vaccination uptake in disrupted societies). The response to infectious diseases requires interventions which could be assisted by adoption of a One Health approach, integrating knowledge and data from animal, human and environmental health domains. This would include the impact of climate and ecological change on the patterns of zoonotic transmission to humans and factors such as changes in vector range and human-animal proximity, human and animal migration and entry to new environments.

Mental health

Mental health was viewed as a strategically important area, particularly in adolescents and young adults in an ever-changing world of new technologies and modes of social interaction. A focus on prevention of mental health problems was considered essential, together with greater understanding of the common environmental and behavioural risk factors and exposures. Mental health was noted as an underrepresented area of the MRC portfolio and a need was identified to re-evaluate the classical framework of prioritising physical health over mental health. Better understanding was also needed on the interaction between physical and mental health in the context of multimorbidities and a move towards a multicomponent view of health.

Environmental change

Environmental epidemiology within the portfolio was considered to be relatively discrete in terms of the wider role environment plays as a key driver of ill health. The panel supported expanding the breadth and expertise of existing investments to establish a strong initiative centred on environmental change (for example, climate change or urbanisation) and its impact on health, especially in LMICs. This area cross-links to infections, health services and resilience as well as to the rising burden of NCDs. Investment in this area would need to consider health implications arising from potential substantial impacts on the availability of food at a global level. Research on building resilience and protecting health-related infrastructures to cope with the consequences of climate change, especially in the Global South, is a priority.

Data science

Underpinning all its identified priority areas, the panel supported the need for increased capacity and capability development in data science and modelling. To meet this need, the panel strongly supported the proposal, made by the MRC Biostatistics Unit, for the creation of an Institute for Biomedical and Health Data Science, with concentrated expertise in methodology and data science including modellers, health economists, computer scientists, machine learning and AI researchers. This would cover methodological work in data science across the whole breadth of the MRC portfolio. The proposed institute would adopt a dual model, with data science methodologists both embedded in domain-specific science areas and having a hub providing close interaction with their peer group. This institute would be discrete from the proposed Institute for Population Health Intervention and Improvement, although they would be expected to work collaboratively and would share a strong basis in methodology. It was also recognised that the data science workforce would require distinct motivation to retain them within the health science sector.

4. Opportunities and implications for the existing portfolio

Comments on the existing portfolio

MRC has appreciable existing centre and unit investments in population health science, epidemiology and cohorts that have made important contributions. The panel agreed that they could also potentially make valuable contributions to the priorities identified here. However, this would require some change and adaptation. As already noted, the current portfolio lacked sufficient strength and depth in implementation science and population- and individual-level interventions. Existing investments through units and centres were also viewed as lacking agility to adapt and respond to take account of new technologies and insights. This was largely due to structural requirements inherent in the traditional conception of such investments that mean they focus on static objectives established at the time of award, with divergence from these being potentially viewed as a failure to deliver.

Many of these investments were established on a model of needing to generate their own data, often through bespoke studies and cohorts, which can constrain the questions they can ask. In this respect they have tended to be stand-alone and largely siloed enterprises that lack rich connectivity and are limited in their ability to draw-in other data streams to fulfil their specified remit. Furthermore, it was recognised that broader engagement was needed between centres and units and large national investments, such as HDR UK and Dementias Platform UK (DPUK), to fully capitalise on potential synergies. The panel noted a significant degree of overlap and recapitulation of activity across epidemiology units within the portfolio, with insufficient investments focused at the implementation end of population science. It was agreed that, in line with an open-science agenda, it would be important for UK population cohorts to be integrated on and available via a single accessible platform (for instance, a federated system) and to share codes and data across units to bridge the gap between smaller cohorts and larger resources.

In the area of climate change research, the panel agreed that the MRC Unit The Gambia at LSHTM and the MRC Centre for Environmental Health were both well-placed in terms of their potential contribution, the former being in a country already being impacted by climate change and the latter having an opportunity to move beyond health impacts of air and noise pollution

Transfer to university unit status

The panel considered the transfer of MRC units to university units at a structural level. Members agreed that the change in status had led to diminished visibility of MRC units. It was recognised that it was harder for university units to interact with other institutions and portfolio investments due to greater administrative hurdles arising from being part of a larger academic organisation. This was viewed as a potential barrier to capitalising on synergies of funding multiple units. For a strategic investment, greater assurance was needed that units continue to serve a national purpose rather than simply merging into the outputs of the host institution. The move away from independence was viewed as having weakened MRC's influence and strategic control. The advantage of the university unit model was noted to be that it provides a more flexible and fluid approach, strengthening integration with university research activity. However, it was considered that the full potential for the increased opportunity for the movement of staff in and out of the unit environment has yet to be realised.

Population and Public Health Domain Panel

- **Chair: Professor Dave Leon** (LSHTM)
- Professor Alan Dangour (LSHTM)
- Professor Cathie Sudlow (University of Edinburgh)
- Professor Daniel Haydon (University of Glasgow)
- Professor Deborah Ashby (Imperial College London) *Partial attendance*
- Professor Dorret Boomsma (Vrije Universiteit Amsterdam) *Apologies*
- Professor Ibrahim Abubakar (University College London)
- Professor Joel Schwartz (Harvard TH Chan School of Public Health)
- Professor Judith Wasserheit (University of Washington)
- Professor Kate Hunt (University of Stirling) *Remote*
- Professor Lijing Yan (Duke Kunshan University, China) *Apologies*
- Dr Manjinder Sandhu (University of Cambridge)
- Professor Mathew Hotopf (King's College London)
- Professor Paul Franks (Lund University)
- Professor Peter Diggle (Lancaster University)
- Professor Susan Michie (University College London)

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