Science? QUESTION TIME

Designing research
to serve ageing populations

Tina Woods

Science QUESTION & TIME?

> " How can we design research to serve ageing populations and those with co-morbidities and ensure that research is reflecting our societal aim of achieving healthy longevity? "

> " We must select the right patients at the right stages of their disease and match them to the relevant therapy. I would expect that in the future patients with neurodegenerative diseases will be managed much like we do diabetes with different drugs given over different times. Most importantly, we all need to work in collaboration. Collaboration between industry, academia, the NHS and clinical researchers is crucial ahead, linking excellent academic research with companies working together in diagnostics and in therapeutics so that we can bring through a new generation of treatments for patients suffering from these awful diseases. The UK is in a very strong position to lead the way. "

> *Dr Fiona Marshall*

## Content

Introduction

The COVID-19 pandemic has created unprecedented strain on health systems and societies around the world. It has shone a light on health inequalities and reinforced the importance of fostering health resilience. It has also highlighted the importance of scientific research to protect the health and wealth of societies.

Science Question Time held on 25 November 2020 brought together leading scientists and policymakers to reflect upon these factors and think about the broader implications for R&D, asking the key question: 'How can we design research to serve ageing populations and those with comorbidities, and ensure that research is reflecting our societal aim of achieving healthy longevity?'

This report communicates key themes and ideas that arose from the discussion and highlights areas for further work, aligned to opportunities in the environment.

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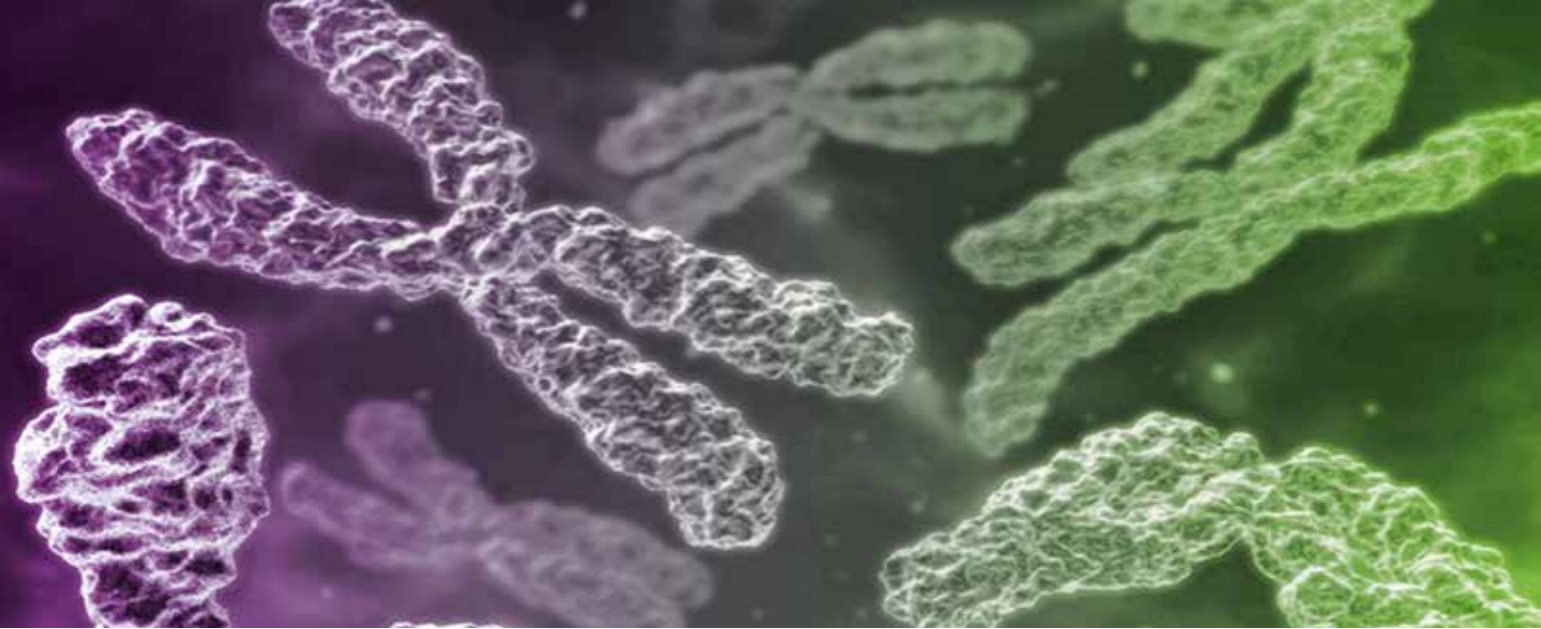
Environmental Context

The COVID-19 pandemic has raised important questions for the UK relating to the state of the nation's health at the beginning of 2020 and the prevalence of risk factors that make individuals and populations more vulnerable to the virus. The Global Burden of Diseases, Injuries, and Risk Factors Study found that Britain had the worst healthy life expectancy in Europe at the beginning of the decade.[1] Even before the pandemic UK healthy life expectancy was falling behind most other European countries – and one of only four countries whose healthy life expectancy declined between 2008 and 2016.[2]

The pandemic has also highlighted how we have taken our health for granted, while exposing the health inequalities that exist in society: the majority of deaths have been in the most vulnerable groups— older populations, those with underlying health problems, in minoritised ethnic groups and/or in deprived communities.[3] Even before the pandemic, data show that people in low-income areas live with ill-health for nearly 20 years longer than those in the highest-income areas.[4] The healthcare challenges that existed before the crisis will remain and will only become more acute, especially with the growing backlog of chronic diseases that have been neglected with so much attention on the virus.

The UK Conservative Manifesto already made a commitment to the goal of delivering five extra years of healthy life expectancy while minimising inequalities ('HLE+5') in health by 2035.[5] This was initially set by the government in 2018 and linked together the objectives of the Industrial Strategy Grand Challenges in AI and Data, Clean Energy, Mobility and Ageing Society[6].

The impact of the pandemic on achieving HLE+5 has not yet been quantified but a report by the House of Lords Science and Technology Select Committee[7] published in January 2021 showed that the government is not on track to meet its key healthy ageing target to ensure people have five extra years of healthy life. The report highlighted the issue of increasing multimorbidity that puts immense pressure on the health system that is not currently set up to treat people living with multiple conditions. It also urges the government to act now in tackling unhealthy ageing and health inequalities. This supports the view from the All-Party Parliamentary Group for Longevity that calls for urgent action to remedy 'our unhealthy nation'.[8]

Scientific developments will form an important part of the remedy to achieve HLE+5 and will also support Britain's ambition to be a socially-responsible scientific superpower.

Early-stage Research and Targeting Early Interventions

The Lords Science and Technology Select Committee report highlights there are many promising advances that may slow the underlying process of ageing and help delay the onset of age-related diseases. The Committee recommends that the Government ensures the UK remains a global leader in drug research and development and that UK Research and Innovation commit to funding further research into the biological processes underlying ageing. The Committee suggests the MHRA should ensure older people are more frequently included in clinical trials and show greater willingness to approve trials which target multiple conditions. Finally, the Committee urges that new data-driven technologies including Artificial Intelligence are harnessed to develop new drugs and identify accurate biomarkers of ageing for personalised interventions to enhance healthier and independent living in old age.

Research into ageing has accelerated in recent years, particularly with the discovery that the rate of ageing is controlled, at least to some extent, by genetic pathways and biochemical processes conserved in evolution that share similarities with cancer. Ageing and cancer are actually two different manifestations of the same underlying process—namely, the accumulation of cellular damage -which is summarised in the nine hallmarks of aging published in Cell in 2013[9].

> "Age is the greatest risk factor for almost all diseases and some of those diseases start much earlier than the symptoms."
>
> *Professor Richard Barker*

Geroscience
Hallmarks of Biological Aging

Genomic Instability
Telomere Attrition
Epigenetic
Proteostasis
Nutrient Sensing
Mitochondrial
Cellular Senescence
Stem Cell Exhaustion
Cell Communication & Inflammation
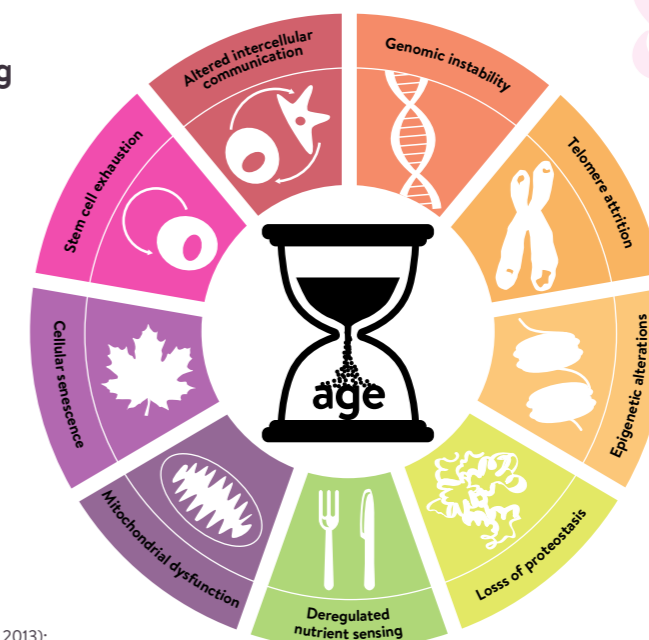
Cell, Carlos López-Otín et al., The Hallmarks of Aging (June 2013):
https://www.cell.com/fulltext/S0092-8674(13)00645-4#secsectitle0010

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Understanding the underlying processes of ageing will be the key to unlocking interventions to address the diseases of ageing, including dementia and other neurodegenerative conditions.

The pharmaceutical industry has invested billions in research to date to identify treatments for Alzheimer's Disease (AD), for example, but the complexity of the underlying biology of the disease explains not only the failure of some trials in the past but also indicates the need for novel drug development paradigms that take into account the prospects of testing multiple therapeutic targets or agents. Such radical changes in clinical trial design and execution, based on the complexity of the disease, will require better understanding of the relationships among the multiple biological processes[10]. This represents one of the grand challenges for future R&D on therapies, however, it is also accepted that it is never too early and never too late in the life course for dementia prevention.[11]

Geroscientists around the world are busy researching interventions to target ageing and age-related disease like AD, including addressing cell senescence, one of the hallmarks of ageing. Senescent cells are fundamental to ageing, and the number goes up as we age. These cells fail to undergo apoptosis or programmed cell death and exist in a 'zombie like' state, turning neighbouring cells senescent as well. The immune system can also undergo senescence, or 'immunosenescence' and this leads to very poor responses to infection and even to vaccination.

"By treating diseases early, even before they manifest, we might be able to treat all these multiple different diseases of ageing. And one key underlying process that we're very interested in is something called cell senescence."

Professor Lynne Cox

New drugs called 'senolytics' kill these cells and can mitigate the effects of ageing. These senolytic drugs are now being tested in clinical trials for several age-related diseases including neurodegeneration.

The ageing process results in multiple traceable footprints, which can be quantified and used to estimate an organism's age. Examples of such 'ageing biomarkers' include epigenetic changes, telomere attrition, and alterations in gene expression and metabolite concentrations.[12] The latest research in ageing biomarkers is exciting, as it is beginning to unravel the complexities of the interplay between genes, environmental factors and, most importantly, the interventions which might minimise risk, delay progression or directly treat age-related diseases including dementia.

There are many different processes occurring in the body that could be used as biomarkers for Alzheimer's disease and other diseases that cause dementia. There is a growing acceptance for the role that inexpensive, non-invasive and more sensitive digital tools can play in monitoring these biomarkers and aid early detection. In the case of dementia, for example, passive technologies could identify changes in the brain 10 to 15 years before symptoms start to impact people's lives. Much of the latest thinking is that if we were to be able to diagnose and treat the disease at an earlier stage, we would be able to potentially slow or delay progression.

So, for example, general fitness and activity levels can be tracked via Fitbit or other walking trackers; people's navigation skills can be identified using the GPS on their phones; changes in social engagement can be captured by how someone talks on their telephone or the language they use in text messages; and measuring fine motor movements can be gauged from how someone navigates a computer screen. There are also ways to assess mood, sleep, memory, gait, and heart rate using digital tools, to create 'digital fingerprints'.

Recently, Alzheimer's Research UK announced a major study, the Early Detection Of Neurodegenerative diseases' (EDoN) with funding from the Bill Gates Foundation to analyse digital data captured from wearable devices such as smart watches to develop these digital fingerprints. AI can be used to identify new insights into the early signals of disease, by combining digital fingerprints with traditional sources such as brain imaging and memory tests.

"Through the EDoN initiative, we want to draw together digital technologies, identify the strongest indicators, and then bring them together in a device or an app that helps us to collect this information passively much, much earlier than we currently do."

Samantha Benham-Hermetz

Dementia highlights how complex the interplay between genes and our environment is, and how individual our risks and responses are to those factors.

Latest research on the 'exposome', for example, shows how lifetime exposure to environmental and socio- economic conditions has an enormous epigenetic impact on people and influences mortality[13]. The 'exposome' represents the complex environmental exposures we are subjected to throughout our lives, including our diet and lifestyle factors, environmental impacts (like air pollution) and social influences, and our body's response to these challenges.

But all this research requires access to high-quality datasets across the lifecourse, including genomics. The power of using technologies like artificial intelligence is looking at the relationship between these biomarkers and understanding the specific reasons why everyone ages differently; once we understand the underlying reasons, we can then begin to design highly personalised interventions as well as population health strategies to help people stay healthier, age better, and live longer.

"Prediction and preventive health care is vastly important for ageing, because in ageing, it is the early life exposures and the longer-term life course lifestyle that trigger the disorders that we have in later life. As part of this we need targeted risk assessment which is about using genomic or other -omics information to assess the risk. This will enable predictive and preventive health care that leads to a healthier ageing because we can detect disease earlier."

Professor Sir Mark Caulfield

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Until recently there was little discussion on taking a life course approach to the science of ageing and healthy longevity but this has started to change and there is now growing interest from healthcare systems around the world, as well as the pharmaceutical industry. There are now well tolerated drugs that are ready here and now for use in older people to improve their health resilience, including metformin and senolytics.

"You start looking at older adults for whom it's a little bit too late to do all those psychosocial interventions. That's where the drugs come in. So, you need a tailored approach at every single point along the life course, but we are starting to tie together the biological causes behind it all."

Professor Lynne Cox

An important component of our future success in developing drugs for diseases of ageing is to effectively translate information coming out of genetics and genomic research into clinical studies. We need to build confidence in our understanding of disease pathways and possible targets using, again, human biology that may be genetics, or studying human disease tissue.

"It's important that we always take time to develop a deep mechanistic understanding of the underlying causes of these diseases with ageing, of course, being the major contributor, and also understanding the time course, and the progression of the disease because different drugs and therapies may work at different times… targeting these pathways offers great hope for finding new therapies."

Dr Fiona Marshall

The Genome UK strategy is focused on creating the most advanced genomic health system in the world for patients. This includes a genomic medicine service in the NHS that will personalise healthcare through pharmacogenomics, that is, choosing the therapy that will most benefit the patient and be least likely to cause harm based on their genetic make-up.

"What if in the future, we could carry around an app on our phone that would allow us to plug in the medicine when our GP or a clinician prescribes it, and test whether we could have it based on our genome."

Professor Sir Mark Caulfield

Clinical Development – Opportunities in a Challenging Area

There is a national policy focus, backed by significant public investment, focused on improving the infrastructure for clinical research in the UK. While this is enormously positive, there are further opportunities relating to reach of the clinical research into the community and into older populations.

In order to effectively develop drugs for the diseases of ageing it is important to translate information coming out of genomic research and into clinical studies. Critical to the success of clinical studies is the use of relevant biomarkers, which can be used to diagnose patients and to track therapies.

"An example of a biomarker we've developed for Alzheimer's is PET tracer that can allow imaging in the brain for a toxic protein called tau that we know accumulates during the disease; using this PET tracer we've been able to show that as tau spreads, it correlates with the symptoms of the disease."

Dr Fiona Marshall

The selection criteria for patients into clinical trials is important. Patients can be stratified, for example, by their genetics or based on imaging or blood biomarkers, but diversity and inclusivity are becoming increasingly important considerations as health inequalities have been starkly exposed by the impact of the pandemic.

"We know that socio economic factors have profound effects on health outcomes but how do we start to build these factors into our basic biological research in order to understand how they're influencing biology? Because if we look at the stark facts, we may say the best way to achieve five extra healthy years quickly is by levelling up agendas and education, rather than through influencing our basic biology"

Dr Alison Cave

One of the learnings from COVID-19 clinical trials is to challenge how much of current trial criteria are absolutely essential, prompting researchers to accelerate the move towards "real world" trials to more broadly represent the patients or communities that they are likely to serve.

"The community primary care setting is a grossly under-exploited opportunity for clinical trials in general."

Professor Sir Robert Lechler

Community-based clinical trials, for example, could take place over a much longer period, and bring in a wider range of people who are affected by diseases to yield different information and insights. For example, in the current situation the very people who would most likely benefit most from anti-ageing drugs are the people who are being excluded from trials because they have multi-morbidities. Healthy people who can get to hospital are not generally the ones who have to self-exclude from trials. We know that elderly people visit their GPs on a regular basis, so we ought to be using primary care infrastructure for setting up trials with people recruited when they go to their doctor; they may have novel ageing testing, and so can have those biomarkers measured.

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"We've been advocating for a new clinical trials infrastructure based on brain health clinics to create a high-quality diagnostic funnel to recruit people at different stages of disease progression into research to collect enriched data about their biomarker status and genetic status. In this way you would have a better range of data about these individuals, and essentially create trial-ready cohorts."

Samantha Benham-Hermetz

""We've got to be a lot more creative about the way we design clinical trials, and the regulatory framework that allows us to do that. We'd love it to come from the Department of Health and CMO, where they're saying care homes would benefit from interventions needed. But we struggled to bring together a consortium for clinical trials in care homes. One of the major problems was around storage of drugs- which had to be in a hospital pharmacy rather than locked in drug trolley that the nurses in the care home could administer and catalogue. Because the drugs have to be administered by hospital physicians, it makes it almost impossible under current regulations to carry out drug trials in care homes. And the other issue that we hit was with consenting."

Professor Lynne Cox

Developments in science are enabling us to be more predictive, and we can potentially intervene earlier if we create 'diagnostic funnels' to find people earlier: for example, the NHS health check could be used in a different way to identify people's risk at a much earlier stage.

The creation of pragmatic trial networks could also be a solution to widen equity and access to earlier diagnosis and participation in clinical trials. But these networks need underpinned by the appropriate data infrastructure, including better data links between secondary and primary care; this will help us to use AI and machine learning to more accurately diagnose disease and bring different modalities of data in to link diagnosis with treatment, and then with downstream public health outcomes. From a regulatory perspective, we need to understand the quality of the data and that sits across care settings, including in the community setting.

"There's a huge opportunity with our NHS to really build a better pragmatic trial network, to enable us to get better answers to some of these questions. This is something that we're definitely looking at within the ISCF challenges: I lead two ISCF challenges associated with data, one of these is Accelerating Detection of Disease you spoke about earlier, and the other is Data to Early Diagnosis and Precision Medicine."

Dr Alison Cave

A Culture of Collaboration

A culture of collaboration between academia, industry, the NHS and government is needed to drive breakthroughs in science. The Academy of Medical Sciences has been leading the discussion on this topic, concluding there is more to be done to facilitate permeability between academia and industry and an ongoing opportunity to engage the NHS in collaborative research.[14]

But collaboration is also needed to address the wider determinants of health to reduce health inequalities. We now know that adverse life experiences can be transmitted to successive generations, and this vicious cycle needs to be broken.

A culture of collaboration will also foster ambitious research and stimulate moonshot thinking in Britain's aspiration to be a scientific superpower

"There needs to be a much better recognition that the science going on in biotech and pharma is cutting edge, absolutely brilliant science. The funders need to be a little bit more creative and risk taking, and the academics need to be a lot more positive about the contribution that the industry can play. And we just need to talk to each other a lot more."

Professor Lynne Cox

"It is time to address these aspects of inequity firmly and completely, because we are at risk of perpetuating a cycle in which some people are completely trapped by the postcode they're born in, or the community they come from. And they cannot escape that"

Professor Sir Mark Caulfield

The UK has significant ambition for public-private partnerships, with initiatives such as the Our Future Health programme (formerly known as the Accelerating Detection of Disease Programme). Our Future Health will be the UK's largest ever health research programme, designed to help people live healthier lives for longer through the discovery and testing of more effective approaches to prevention, earlier detection and improved treatment of diseases.[15]

Specific areas for exploration in the field of ageing were discussed in the Science Question Time event. In particular, the idea of a Dementia Moonshot and an Open Repository for Ageing Biomarkers were cited are areas for exploration:

Conclusion

Premature and avoidable ill health degrades people's lives, local communities and their economies. Far more wellbeing and health can be gained by preventing illnesses than by treating them. Indeed, prevention will always be better than the best treatment.

Very early on it was clear that COVID-19 does not treat all age groups equally, and that many of the expected interventions such as vaccines and treatments will not work as well in elderly people.

We have seen that the most exciting advances in improving health resilience include tackling the underlying biological processes of ageing. COVID-19 has created the economic case for investment in healthy ageing, collecting better data on healthy ageing, and the critical role of technology in the quest to rebuild health and economic resilience post COVID-19.

While AI is being harnessed to accelerate research into vaccines and treatments for COVID-19, so should it be applied to help prevent chronic diseases, as well as ageing itself, to keep us healthy for longer. Research into ageing biomarkers is expected to furnish important insights into how we can stay healthy and measure the effectiveness of interventions targeting the wider determinants of health.

The ambitions we have for science and the ambitions we have for society need to be more cohesive at a UK policy level. The UK wants to lead the world in scientific innovation. The UK Government is also committed to levelling up across the regions, and the focus on health inequalities within this should be first and foremost. To truly enable healthy longevity, there are clear interdependencies with a thriving science base – one in which both early and late stage R&D are fully supported.

There are responsibilities for policy makers and researchers alike to act upon – research should be reflective of societal goals, by being inclusive, patient-centric and collaborative. Funding for scientific research and data collaborations should be shared more equitably outside the 'golden triangle.' Policy makers need to foster an environment for inclusive innovation around a 'common cause'.

Health inequalities increase with age, so a focus on health inequalities and health resilience (at both a personal and systemic level) will be perhaps the most significant driver of healthy ageing.

> "We have found during this terrible year of Covid that health resilience is more important than ever. We know that sadly, the UK population is, on average, unhealthier than many other comparable countries in Europe, and doing something about that would not only make us more resilient towards Covid, but actually give us a much better quality of life for much longer. So, there are clearly important steps that need to be taken and need to be taken urgently."
>
> *Rt Hon Damian Green MP*

Dementia Moonshot

It is expected that developments in neurodegeneration will leapfrog in the way that cardiovascular health has. A public-private initiative could accelerate this further by looking at the application of biomarkers, data, new types of trials, interaction with other morbidities, and new populations such as care homes. Creating pragmatic trial networks could form part of the vision for a Dementia Moonshot alongside early stage investment in translational medicine.

> "We can see across many industries how data and digital tech have completely transformed how we understand different networks, how we understand different systems. And I think the one area where we haven't made most of that is in health. It's acted as a disruptor in so many other industries. And I think health is ripe for this."
>
> *Samantha Benham-Hermetz*

Open Repository for Ageing Biomarkers

In the field of healthy longevity there is significant interest in data collaboration in the area of biomarkers to enhance AI-driven research. This would also collect data about older people and those multi-morbidities in the context of building up resilience to COVID-19 and future pandemic threats.

> "There's some really exciting work in persuading endogenous tissues to regenerate. The other area is multi-morbidity. We don't understand well enough why some diseases co-cluster, though do understand some, with insulin resistance being one sort of common pathway. But we don't understand all and one that I'm particularly preoccupied with is the mind-body interface."
>
> *Professor Sir Robert Lechler*

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Further work

This Science Question Time event has prompted much discussion in areas ripe for further policy debate and agreement.

We would like to continue the discussion by sharing this report with the Science Minister, the Science and Technology Committees in both the Commons and the Lords, as well as the APPG for Longevity.

Our view is that the following areas are key to explore through a science of ageing lens:

- Inclusive Innovation, with scientific research and development at the core, will be a vital component of the levelling up agenda. Diverse data sets for research purposes and inclusive strategies for clinical trial participation will help to reflect real world priorities in areas of high unmet need, including diseases of ageing.

- Further exploration of the enablers of inclusive innovation is needed and should be seen as an agenda for UK leadership.

- There are many excellent examples of scientific collaboration in the UK, but further collaboration across industry, academia and the NHS could be achieved if there was more permeability.

  Further exploration of policy levers to facilitate greater scientific exchange across industry, academia and the NHS will be important

to explore. Research in the field of ageing and diseases of ageing is a great example of where scientific collaboration works well; it is equally an area with great potential for further collaboration.

- The Office for National Statistics (ONS) Health Index[16], currently out for government consultation, could provide a means of assessing and valuing the health of the nation in a comprehensive way, targeting geographical and cross-governmental areas (including education, housing etc) where support is needed most to level up on health.

- Measuring health across the lifecourse and having a benchmark for progress will be important – measuring access to innovation and participation in research (across all segments of the population) are important metrics to consider.

- The UK's significant ambitions in relation to global scientific leadership, healthy longevity and achieving a more equal society need to be cohesive at a policy level. Delivery on an aligned ambition requires leadership and coordination efforts from The Office for Life Sciences, involving the health/life sciences sectors, with close scrutiny in Parliament.

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