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Precision prevention for modifiable health risks: Steps to achieving personalised preventive healthcare

Summary report of a FORUM workshop held 11 December 2020

The Academy of Medical Sciences

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All web references were accessed in February 2021.

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Executive summary

The NHS Long Term Plan envisages a health service that prioritises prevention as well as treatment, to keep people in good health and to minimise demands on health services. This vision will depend on an ability to identify risk of disease, so that preventive measures can be targeted according to risk profiles and tailored to their specific needs – this is known as 'precision prevention'.

Risk stratification is already core to NHS practice. Now, however, a range of new technologies are providing exciting opportunities to stratify populations with greater granularity and for a wider range of diseases. Genomic profiling can reveal disease predispositions, and genomic information is increasingly being used to guide NHS care. In addition to genomics, other 'omics' technologies (transcriptomics, proteomics, metabolomics and others) also offer great potential to identify those at increased risk of developing particular diseases.

Additional opportunities to refine risk assessments are also arising from the analysis of routinely collected health data. Analysis of the wealth of health and demographic data in electronic health records and other sources of health data can identify factors associated with poor health outcomes, again enabling high-risk individuals and groups to be distinguished.

In theory, precision prevention should lead to improved health outcomes and better use of NHS resources. The Academy of Medical Sciences' FORUM workshop held on 11 December 2021 explored some of the challenges preventing the promise of precision prevention being realised, particularly two critical bottlenecks: 1) the assessment of cost-effectiveness; and 2) the implementation of new technologies within the NHS.

Cost-effectiveness analyses generally aim to estimate projected net health benefits. However, for prevention, impacts on health outcomes are likely to take several years to materialise, and will be dependent not just on the performance of a predictive tool but also on its use by clinicians and the effectiveness of preventive interventions. It is therefore difficult to rely solely on the results of randomised controlled trials to generate the necessary evidence on the impact on health outcome and health care costs. Furthermore, product development is primarily driven by small companies and start-ups, which typically do not have the resources to carry out large and long-term studies. A requirement to generate trial evidence on outcomes before income is realised acts as a significant deterrent to innovation.

A further challenge is that current regulatory and health technology assessment paradigms are based on a 'one disease, one test' model, whereas 'omics technologies have the potential to screen for predispositions to multiple conditions.

Several important **implementation barriers** were identified. These include a lack of dialogue between developers and clinicians, such that product design is often technology-driven and does not take sufficient account of practical constraints that limit the take up of innovations

within the health service. Low levels of digital maturity in the NHS – fragmented and outdated IT systems, information system management and staff practices – as well as a risk-averse and change-averse culture within the health system are also critical obstacles to the adoption of new technologies.

Discussions identified a range of ways in which these challenges could be addressed:

- **Bringing clinicians, developers and patients closer together**: Development of target product profiles could provide developers with a clearer sense of clinicians' and patients' needs, while collaborative R&D partnerships could ensure that product design better reflects clinicians' and patients' preferences. Early engagement with patients is needed to ensure that new tools are acceptable to and meet the needs of patients.
- **Risk sharing and innovative financial models**: Closer public–private engagement and better risk and reward sharing could incentivise new product development and ensure that it is driven by unmet medical needs. Collaborative approaches could address the challenges of evidence generation on outcomes of risk-prediction tool and their associated preventive interventions.
- **Developing fit-for-purpose assessment processes**: Greater flexibility is needed in technology assessment, to take account of the challenges in generating health outcome data and use of tests of multiple variables. Possible ways forward include greater consideration of economic modelling data on potential impacts early in development, use of a wider range of data, including routinely collected health data, and conditional recommendations dependent on further data collection. Innovative trial designs could help provide comparative data and greater insight on outcomes.
- **Creating an environment to accelerate innovation**: 'Test beds' could be established for the piloting of new technologies and collection of observational data, as well as for exploring implementation challenges. Pilot sites could be established to explore the possibility of system re-engineering for high-value but disruptive technologies.

The nationwide coverage of the NHS, the UK's scientific strengths and high levels of digital technology usage make the UK an ideal country to lead developments in precision prevention. There is great potential for a 'win–win–win' scenario – improved health outcomes, more effective use of healthcare resources, and high-value job creation and innovation with global application.

Realising the potential of precision prevention will require a partnership between the private and public sectors to create an environment that nurtures innovation targeting unmet healthcare needs. This will require a clear strategic vision that places precision prevention at the heart of the future health system.

This meeting was convened as part of the Academy's FORUM programme, which was established in 2003 to recognise the role of industry in medical research and to catalyse connections across industry, academia and the NHS. We are grateful for the support provided by the members of this programme and are keen to encourage more organisations to take part. If you would like information on the benefits of becoming a FORUM member, please contact FORUM@acmedsci.ac.uk.

Introduction

The NHS Long-Term Plan[1] outlines a paradigm shift in healthcare, from today's treatment-focused approach to healthcare that is predictive, preventive, personalised and participatory (the 4Ps).[2] In part, this reflects the UK's ageing population, which has a higher risk of multiple long-term conditions, presenting major challenges to the sustainability of the health system. In addition, scientific and technical advances are providing opportunities to better understand how factors such as concurrent conditions, genetics, lifestyle factors, and social and environmental determinants influence the risk of developing disease, creating opportunities for more targeted and tailored disease prevention – which is known as precision prevention.[3] In theory, this should lead not just to improved health outcomes but also to more effective use of healthcare resources.

Risk prediction tools are already commonplace in clinical practice, drawing on a wide range of readily available data (sex, age, BMI, blood pressure) and test results. However, new technologies offer the prospect of more refined tools with greater predictive power, as well as expansion of risk prediction into new therapeutic areas. Among the scientific advances driving the development of these tools are the **'omics' technologies** (see Box 1), which provide detailed information about individuals' genetic make-up, biochemical processes and metabolism, and their association with the risk of particular diseases.[4]

Box 1 - 'Omics' technologies

A range of high-throughput 'omics' technologies can provide insight into patients' physiology and risk of disease. They share the common feature that multiple biological factors are characterised at the same time, but differ in the factors being characterised:

Genomics: Genes, providing information on genetic predisposition.

Transcriptomics: RNA, providing information on gene activity/expression.

Proteomics: Proteins, providing information on the key molecules that control the biology of cells.

Metabolomics: Cellular metabolites, providing information on the enzymatic activities and biochemistry of cells.

As well as their use individually, there is also growing interest in combining them in 'multi-omics' approaches to provide a more comprehensive description of biological systems and health states.[4]

[1] NHS. (2019). *The NHS Long-Term Plan*. https://www.longtermplan.nhs.uk

[2] Hood L *et al.* (2004). *Systems biology and new technologies enable predictive and preventative medicine.* Science. **306**:640–43

[3] Gillman MW & Hammond RA. (2016). *Precision Treatment and Precision Prevention: Integrating "Below and Above the Skin"*. JAMA Pediatr. **170(1)**:9-10

[4] Olivier M *et al.* (2019). *The need for multi-omics biomarker signatures in precision medicine* Int J Mol Sci **20(19)**:4781

Incorporating 'omics' information could deliver refined risk-prediction tools that more effectively stratify patient populations according to risk. Attention could then be focused according to risk profiles, combining generic preventive approaches with targeted measures linked to the specific nature of their underlying risk. Potential benefits include early detection of enhanced risk to support timely primary prevention, as well as more tailored secondary prevention after initial events, or prevention of secondary complications (such as those affecting people with diabetes). As well as the scientific drivers of novel tool development, there remains huge unmet need in many common therapy areas, such as cardiovascular disease (Box 2).

More accurate risk stratification would also reduce the use of interventions among those at lowest risk, sparing patients from unnecessary procedures and anxiety, and ensuring that use of healthcare resources is concentrated on those in greatest need.

Pioneering work in this field has been carried out in genomics, particularly in the areas of cancer and rare diseases.[5] Whole genome sequencing of unexplained cases of congenital syndromes, for example, increased diagnosis rates by 20–25%, while up to half of cancer genome sequences are generating actionable information. While genomic results are currently used mainly to guide treatment or care, there is also great potential to use genomic information for prevention; for example, to generate polygenic risk scores or to identify risk loci that indicate the need for preventive interventions.[6,7]

A second key technological advance is **health informatics** – the use of routinely collected health data to provide additional insights into disease risk. Linkage and analysis of large-scale data sets can provide insights into health, environmental, demographic and lifestyle factors associated with poor health outcomes. There is also the long-term prospect of integrating 'omics' and healthcare data to generate personalised risk profiles.

It should be emphasised that precision prevention is complementary to, rather than a replacement for, traditional public health interventions to safeguard health. Such traditional interventions generally take a population-wide approach, although there is interest in applying them in a more targeted fashion – precision public health.[8] However, there are concerns that too great a focus on 'precision' could detract attention from upstream population-wide factors that have far larger impacts on health and health inequalities.[9] In addition, it must be acknowledged that the effectiveness of prevention will depend fundamentally on the communication of risk and, often, the modification of behaviour (issues not discussed in detail at the workshop).

For the vision of precision prevention to become a reality, there is a need to move beyond proof of principle and consider how these new technologies and applications can be introduced into the health system. For this to happen, new tools must secure approval from regulators such as the Medicines and Healthcare products Regulatory Authority (MHRA) and they must be endorsed by health technology assessment bodies such as the National Institute for Health and Care Excellence (NICE). They must also overcome barriers to the adoption of new

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[5] Turro E *et al.* (2020). *Whole-genome sequencing of patients with rare diseases in a national health system.* Nature. **583(7814)**:96-102.
[6] Scott RH *et al.* (2019). *Genomic medicine: time for health-care transformation.* Lancet. **394(10197)**:454-456
[7] Claussnitzer M *et al.* (2020). A brief history of human disease genetics. Nature. **Jan;577(7789)**:179-189.
[8] Khoury MJ *et al.* (2016). *Precision Public Health for the Era of Precision Medicine*. Am J Prev Med. **50(3)**:398-401.
[9] Taylor-Robinson D & Kee F. (2019). *Precision public health-the Emperor's new clothes*. Int J Epidemiol. **48(1)**:1-6.

technologies and ways of working within the health service.

To meet these demands, product developers need to provide evidence of safety, performance and, crucially, cost-effectiveness. However, given the change in paradigm presented by precision prevention, it is not always clear what evidence is required and how it should be generated. And while evidence is necessary, it is seldom sufficient to achieve uptake within health systems. In plenary presentations and breakout groups, the Academy of Medical Sciences' FORUM workshop, co-chaired by Professor Katherine Payne, Professor of Health Economics at the University of Manchester, and Professor Sir John Tooke FMedSci, Professor of Medicine at University College London and Co-Chair of the Centre for the Advancement of Sustainable Medical Innovation (CASMI), addressed these critical challenges and how they might be overcome.

[10] Olivier M *et al.* (2019). *The Need for Multi-Omics Biomarker Signatures in Precision Medicine.* Int J Mol Sci. **20(19)**:4781.

Box 2 - Stratified cardiovascular care

Despite much progress, cardiovascular disease (CVD) remains the world's biggest killer, responsible for 18 million deaths annually, one-third of which occur prematurely in people under the age of 70.

Multiple risk factors for CVD have been identified, spanning biological measures and genetics to health behaviours and environmental factors. Many algorithms already exist to stratify populations according to their risk of cardiovascular events. Typically, these risk scores perform poorly in individuals and are dominated by unmodifiable risk factors, such as age and sex.

Refining risk scores, by including 'omics' and novel biomarkers derived from routine clinical images (e.g. using artificial intelligence), has the potential to target risk reduction measures to those who are more likely to benefit from them. This population includes a proportion of younger individuals and women who would be deemed at 'low risk' according to conventional algorithms.

Modest average risk reductions over the relatively short follow-up of conventional clinical trials have frequently prevented the adoption of new cardiovascular drugs by health systems and deterred industry's investment in CVD. Improved risk stratification may facilitate the development of new treatments in different ways. Application of new technologies can help in the selection of patients who are more likely to benefit substantially from risk reduction measures, whereas genomic profiling may identify individuals who will exhibit a greater response to particular treatments (or are likely to experience serious side-effects).

In the UK, there are now unprecedented opportunities to run cost-efficient clinical trials in partnership with the NHS, making use of health data for patient recruitment and long-term follow-up. Combining more refined risk stratification with more efficient trial design and delivery would position the UK as an international hub of industrial and academic partnership for R&D in CVD and other common diseases, and lead to increased patient access to new life-saving treatments and prevention.[9]

Effectiveness, economics, and implementation

The translational journey for a novel risk prediction tool requires the demonstration of not only effectiveness, but crucially cost-effectiveness. Without this key metric, its route to adoption will be difficult, but acquiring the correct data, and undertaking the key analyses are themselves significant challenges. Even once cost-effectiveness has been demonstrated, the adoption and implementation of a novel tool into clinical pathways can be protracted and inconsistent. Given the time and capital investment required to support the development of a novel risk tool, taking it from concept to adoption is a challenging path.

Cost-effectiveness is key

To be used in the NHS, new risk prediction tools should ideally receive a series of regulatory and health technology assessment approvals. The first of these is from the MHRA, which focuses primarily on the safety and performance of medical devices such as diagnostic tools. Software and apps that underpin some risk prediction tools can also be categorised by the MHRA as medical devices if they are used in a clinical setting.

A second and potentially more problematic hurdle is the need to demonstrate **cost-effectiveness** as part of a health technology assessment. Without evidence of cost-effectiveness, products are unlikely to be recommended by NICE and considered for use within the health service.

Cost-effectiveness analyses aim to quantify anticipated consequences, in terms of health outcomes, taking into account negative unintended consequences (harms) and costs to the health care system. Cost-effectiveness analyses are underpinned by the concept of opportunity cost (what was not achieved because resources were devoted instead to the intervention or device being assessed). The results of cost-effectiveness analyses provide a measure of **'population net health benefits'**, so the cost-effectiveness of tools can be compared with each other and with current practice.

In practice, these assessments are highly complex. For example, assessment of a risk stratification tool must consider the impact of false positives (leading to unnecessary treatment and costs) and false negatives (leading to false reassurance and delayed treatment). Impacts will depend on both the performance of the device (its specificity and

sensitivity) and the consequences of false positives and negatives.

From the developer's perspective, demonstrating impact on health outcomes is highly challenging. For a start, health impacts are likely to be long term, given that the aim is to prevent diseases that often take years to manifest. In addition, health impacts are dependent not just on the tool but also on how it is used by clinicians: if a clinician chooses not to follow a course of action indicated by use of a predictive tool, the health benefits of that tool may be underestimated.

Health outcomes will also depend on the impact of preventive interventions that are selected on the basis of test results. These interventions may aim to change patient behaviour, which a risk stratification tool has little capacity to influence. Technologies that can track the impact of preventive interventions (Box 3) and subsequent change in risk could help empower patients and clinicians to adopt tools. Cost-effectiveness is also not set in stone – development of a more effective preventive intervention, for example, could have a significant impact on a tool's cost-effectiveness. Indeed, use of a risk stratification tool could itself drive the development of improved methods of prevention in target populations, as discussed for cardiovascular medicine above (Box 2).

For pharmaceuticals, companies typically provide data on clinical outcomes from phase III trials to support cost-effectiveness analyses. However, such studies are less feasible for prevention, when impacts are expected years or even decades in the future. Furthermore, medical device companies are generally smaller and without the financial resources to fund the kind of large clinical trials needed to generate outcome data.

A further challenge is that cost-effectiveness analyses are typically based on a 'one disease, one test' paradigm, with diagnostic tools being used to detect risk factors for a single condition. However, one of the advantages of 'omics' technologies is that they provide a platform able to offer information on risks of multiple conditions in a single analysis. They are also in continual development, as more disease associations are discovered and tests are updated.

Additional issues include the fact that differing stakeholders, such as service commissioners, clinicians and patients, may have differing perceptions of the value of benefits provided by better risk prediction. In addition, it may take time for the full value of a new tool to be realised, as its use becomes embedded and clinicians optimise its contribution to clinical practice and begin to fully exploit its capabilities.

[11] Williams SA *et al.* (2019). *Plasma protein patterns as comprehensive indicators of health.* Nat Med. **25(12):**1851-1857
[12] Yang J *et al.* (2020). *Impact of Kidney Function on the Blood Proteome and on Protein Cardiovascular Risk Biomarkers in Patients With Stable Coronary Heart Disease.* J Am Heart Assoc. **9(15)**:e016463.
[13] Corlin L *et al.* (2021). *Proteomic Signatures of Lifestyle Risk Factors for Cardiovascular Disease: A Cross-Sectional Analysis of the Plasma Proteome in the Framingham Heart Study*. J Am Heart Assoc. **10(1)**:e018020.

Box 3 - Proteomics for disease prevention

Genomic approaches have been highly successful at identifying inherited genetic risk factors for disease. However, genes exert their effects primarily through the proteins they encode, and their effect will depend on how actively they are transcribed and translated into proteins. Environmental factors are also downstream from genetics. The presence or levels of proteins may therefore be better indicators of health status and future risk. A further advantage is that the impacts of preventive interventions can be monitored by tracking changes in protein levels.

The disadvantage of protein-based approaches is that simultaneous measurement of many proteins is much more difficult than for DNA. Technologies such as that developed by Somalogic and presented at the workshop have been developed to combine the powers of proteomics-based analyses with the ease of DNA-based manipulation. Its platform is based on the use of DNA 'aptamers' – fragments of DNA that have antibody-like recognition properties and so can hook out specific proteins from a sample of blood or other biological material. Extracting and analysing protein-bound aptamers can therefore reveal which proteins were in the original sample and at what concentrations.

By analysing samples from patients with different conditions, the protein 'signatures' indicative of a wide range of conditions, multiple physiological parameters (such as kidney function, lean body mass and glucose tolerance), and even high alcohol intake can be identified.[11-13] These assessments are, in general, as least as good as current gold standard clinically-used assays. Through collaborations with population cohorts, the research undertaken by Somalogic has been able to track how protein levels change as diseases develop, revealing early signatures of elevated risk.

The tests can also be used to identify physiological changes linked to interventions, for example those that occur during weight loss, illustrating their potential to be used to track the underlying impacts of interventions. One particular use of this technology could be in assessment of complex or difficult-to-stratify patients. As well as providing more refined risk assessments, test results could also highlight specific disease manifestations or physiological traits that warrant special attention.

The challenges for developing such technologies include a health economic paradigm based on single tests and the demand for outcomes data before payors commit to investment. Large randomised controlled trials to obtain outcome data could be difficult for a start-up company to justify financially. Furthermore, use of the technology opens up enormous potential to experiment with different prevention strategies, the impacts of which would take years to determine.

From evidence to implementation

Even if a new device achieves regulatory approval and makes a compelling case for cost-effectiveness, it may still not be taken up by health systems. A range of obstacles exist to the implementation of new technologies in the NHS. One of the most important is the lack of 'fit' between a new technology and current systems and working practices. If a new technology requires major shifts in practice and the established care pathway, or is incompatible with current technical infrastructure, it is unlikely to be introduced unless it offers very great improvements over current approaches.

In part, this reflects the tendency of developers to take a technology-led approach, seeking to identify potential uses of an innovative new technology within the health system. As a result, they may pay less attention to practical implementation barriers, while lack of engagement with health service staff may mean there is no opportunity for users to communicate desirable features or system constraints that could influence uptake.

The degree of digital maturity in the NHS can also be an important obstacle. Variation in IT systems or legacy systems may represent technical barriers, while management of institutional information systems and the prevailing culture surrounding digital technology use may slow the introduction of new tools.

Further challenges include institutional inertia and risk aversion, which can make any change difficult to implement, particularly in settings of high service demand and limited spare capacity, and where there are few incentives to change working practices. For applications based on clinical data, the quality, completeness and representativeness of data may also be of concern to clinicians and discourage uptake or reliance on results.

Next steps to supporting innovation

Despite these challenges, the dual drivers of unmet clinical need and emerging, innovative approaches are leading to the development of novel risk prediction tools. To support their development and translation, a number of steps could be taken to maximise their chance of success and speed up their adoption.

Discussions identified a range of ways in which these challenges could be addressed.

Target product profiles

Target product profiles (TPPs) can aid developers by providing a clear specification of the essential and desirable features of products to meet clinical needs. As well as technical performance, they can include specifications related to integration with existing systems and working practices. Collaborative consensus-based development of TPPs, involving researchers, clinicians, developers, patient representatives and others, can ensure that the needs of a range of stakeholders are taken into account. Engagement with regulators during TPP development can also ensure that evidence needs are considered early in development.

Closer engagement with users and patients

Earlier and stronger engagement between developers and users – healthcare staff – can ensure that clinicians' priorities feed into new product development and that product design reflects and can be built into everyday working practices. Involving patients in product development may also be important to ensure that new tests meet their needs and that are willing to act on their results. Product development may need to consider how to integrate risk communication, to support effective patient–clinician dialogue and shared clinical decision-making.

Risk sharing and innovative financial models

Tools to aid disease prevention have the potential to be cost-effective and possibly cost-saving. However, investment in new diagnostic and risk stratification technology development may not be commercially attractive. Innovative financing mechanisms may be needed to provide incentives for innovation in areas of identified need.

In addition, a 'catch-22' situation currently exists, where it is difficult to gather data on cost-effectiveness without implementation but challenging to implement without cost-effectiveness data. With the medical device marketplace dominated by small companies and start-ups, it is unrealistic to expect the commercial sector to invest in outcome studies for products that will not generate the same returns as pharmaceuticals. Some form of collaborative development of evidence or risk sharing, for example public-private partnerships, might be needed to address the cost-effectiveness hurdle.

Early economic analyses

Given the challenges of generating outcomes data through randomised controlled trials alone,

a more flexible approach to evidence assessment may be required. Decision-analytic modelling of possible health gains and cost implications could provide insights into potential cost-effectiveness at an early stage of development and underpin further support for promising technologies. Decision-analytic modelling could also explore the impacts of uncertainty in different model parameters and shed light on the factors that have most influence on overall cost-effectiveness.

These insights could be used to inform research agendas to gather data to reduce uncertainties and provide more robust estimates of cost-effectiveness. Use of such approaches would need the support of agencies involved in health technology assessment such as NICE.

Use of publicly funded test beds

Diagnostics and risk stratification tools operate in a complex clinical environment, informing but often not dictating clinician decision-making. Their full impact is therefore difficult to ascertain without use within health systems. Population cohorts could be used as test beds in which use of new technologies are evaluated in a controlled setting, potentially as part of a risk sharing mechanism. Test beds could also be used to pilot and refine innovations at early stages of development.

NHS/registry-embedded trials

It is also possible to carry out clinical trials embedded within health systems, including primary care, with data collection through electronic health records. This could allow for collection of data through, for example, cluster randomised controlled trials comparing areas introducing new tools and those offering usual care.

Innovative trial designs

Other innovative trial designs may be able to gather outcome or other important data. Variation in the timing of introduction of innovations in different regions could be exploited to provide comparative data; more formally, a stepped wedge design could be used during an implementation phase, so high-quality data could be gathered from both intervention and non-intervention areas. Emerging trial designs, including 'umbrella' or 'basket' trials, could also be used to test multiple approaches simultaneously.

Greater use of conditional recommendations

An alternative or complementary approach would be to mimic the conditional approval mechanism for pharmaceuticals, in which approval for use is dependent on a further phase of data collection in advance of a definitive decision. A conditional recommendation could be based on decision-analytic modelling – combining multiple sources of evidence to provide estimates of costs and outcomes - (see 'Early economic analyses' section above) or limited clinical data, with reviews then assessing how well real-life performance matches the predictions of models.

Enhancing clinical utility of data

Decision support tools based on routinely collected health data could contribute to patient stratification and development of more tailored prevention programmes for patients. A common concern about such approaches relates to the completeness, accuracy and representativeness of clinical data. However, as the value of data aggregation and analysis increases and becomes more clinically useful, this should create a virtuous cycle encouraging greater fidelity in data entry.

Incentivising innovative use of new information tools

New diagnostic and data-based tools should address a specific medical need, but may have greater potential to improve patient outcomes, healthcare processes or the patient

experience. Ways need to be found to encourage clinicians to explore potential innovative uses of new tools and platforms in a safe and supportive environment.

System re-engineering for disruptive technologies

Occasionally, new technologies may emerge that offer a step change but do not fit easily within existing working paradigms. Mechanisms such as 'pathfinder sites' could be established to allow disruptive technologies with great potential to be piloted, to gain evidence not only on outcomes but also on practical implementation.

Conclusion

The workshop co-Chairs, Professor Katherine Payne, Professor of Health Economics at the University of Manchester, and Professor Sir John Tooke FMedSci, Professor of Medicine at University College London and Co-Chair of the Centre for the Advancement of Sustainable Medical Innovation (CASMI), closed the workshop by reflecting on how the potentially bright future of precision prevention might be made a reality.

The nationwide NHS, the UK's scientific strengths and high levels of digital technology usage make the UK an ideal place to lead developments in precision prevention. There is great potential for a 'win–win–win' scenario – improved health outcomes, more effective use of healthcare resources, and promotion of innovation with global application. Precision risk prediction tools are already showing their value in predicting and preventing ill health (Box 4) and these successes should be built upon.

Realising this potential will require a partnership between the private and public sectors to create an environment in which innovation targeting unmet medical needs can flourish. Currently, the UK continues to pioneer the development of new technological solutions, but health technology assessment processes geared around the pharmaceutical model are proving an obstacle, not enabling their potential value to be realised.

More flexible approaches to evidence generation are needed that reflect the realities of the medical device marketplace and the challenges of assessing preventive technologies. Processes also need to move beyond the 'one disease, one test' model to accommodate testing of multiple variables and multi-omics analysis.

Test beds or pathfinder sites within the NHS may provide opportunities for productive public–private partnerships and risk sharing, through 'phase IV'-like piloting and effectiveness studies that use routinely collected health data as intermediary steps in the pathway towards beneficial outcomes. These kinds of studies could also provide opportunities to identify and address implementation barriers, an important bottleneck to the introduction of new technologies in the health system.

More generally, there is a need to ensure that diagnostic and risk stratification tools are valued within the health system. More economic modelling of their potential impact could help to drive greater interest and stimulate a demand from the health system for such tools. A greater focus on outcomes rather than processes within the health service could similarly incentivise adoption of preventive measures.

Ultimately, encouraging greater use of risk stratification and preventive technologies must form part of a wider culture shift in the health service, away from a primary focus on treatment of disease and towards the safeguarding of good health. This will not only be better for people's health but will also contribute to the long-term sustainability of the health system. Through its Genomics England programme, the UK pioneered the medical application of genomics research and integrated genomics technologies into the NHS. It now has the opportunity to make an equally bold initiative to ensure that the potential of the full range of

'omics' technologies and health data applications transform healthcare in the UK.

[14] Clift AK *et al.* (2020). *Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study.* BMJ. **371**:m3731.
[15] https://digital.nhs.uk/coronavirus/risk-assessment/clinical-tool
[16] https://qcovid.org/

Box 4 - QCOVID: COVID-19 risk stratification

With very little data to work with, early efforts to identify those at risk of poor COVID-19 outcomes were based on expert opinion and consensus, which underpinned development of the shielded patient list. As more cases were reported, it became clear that a more diverse range of patients were dying of COVID-19, and a team led by Professor Julia Hippisley-Cox was tasked with developing a 'living prediction' model that could incorporate new data as it emerged to better identify those at highest risk of poor outcomes.

The QCOVID model was conceived as a tool to support communication with patients about their relative level of risk and to stratify and prioritise populations for interventions, including vaccination.[14,15] It could also stratify patient groups for clinical trials.

The QCOVID model was based on data from a representative sample of GPs' electronic health records, covering 20% of the UK population. These data were linked to multiple other data sources, from disease registries, intensive care units, test data and other sources.

The data were divided into two sets, one being used to develop the model and one being used as a validation data set. A further validation was carried out on an independent data set, the ONS public health data asset, generated in response to COVID-19, which covers 40 million people.

The model showed excellent predictive power, with the top 5% of the population identified as being at highest risk accounting for 75% of all deaths, and the top 20% making up 94% of all deaths.

QCOVID has been incorporated into a living systematic review of COVID-19 and was identified as having particularly low risk of bias. It placed great emphasis on transparency, and a web-based calculator was developed that implements the algorithm and is available for research use.[16] An NHS version with linkage to other data sources is in routine clinical use. The model is updated as new data emerge and as factors change the risk of disease (such as the roll-out of vaccination).

The QCOVID is an extension of other similar tools developed by the team for other conditions such as cardiovascular disease, and the approach adopted for COVID-19 could be applied to additional diseases to support patient stratification and aid clinician decision-making.

Annex I - Agenda

Friday 11 December, 13.00 – 17.00	
13.00 –13.20	**Introduction and framing presentation: The opportunities and challenges of precision prevention technologies** Professor Katherine Payne, Professor of Health Economics, The University of Manchester Professor Sir John Tooke FMedSci, Professor of Medicine, UCL & Co-Chair, Centre for the Advancement of Sustainable Medical Innovation (CASMI)
	Session 1: The clinical applications of predictive technologies
13.20 – 13.30	**Exemplar disease area: The unmet need of cardiovascular disease – where are the opportunities of predictive technologies?** Professor Barbara Casadei FMedSci, British Heart Foundation Professor of Cardiovascular Medicine, University of Oxford
13.30 – 14.30	**Panel: Comparing the potential value proposition of technologies (Development, Evaluation and Implementation)** Professor Sir Mark Caulfield, Chief Scientist, Genomics England Dr Stephen Williams, Chief Medical Officer, SomaLogic Professor Julia Hippisley-Cox, Professor of Clinical Epidemiology & General Practice, University of Oxford
	Session 2: Evaluating predictive technologies
14.30 – 14.45	**Presentation: Evidence needs for evaluating predictive technologies** Professor Mark Sculpher, Professor of Health Economics, University of York
14.45 – 15.00	**Presentation: How do we gather evidence and who should be involved** Professor Neil Hawkins, Professor of Health Economics and Health Technology Assessment, University of Glasgow
15.00 – 15.10	**Break**
15.10 – 16.10	**Breakout group discussion: The pathway for development, evaluation and implementation of precision prevention technologies** Attendees will be divided into smaller groups to discuss: • What evidence is needed to establish effectiveness and value of a predictive technology for clinical decision making and thus patient outcomes? • How do we support the implementation of cost-effective technologies into clinical pathways?

	Session 3: Next steps for forming a precision prevention pathway
16.10 – 16.50	**Plenary discussion: Next steps in development, evaluation and implementation** The Chairs will facilitate a plenary discussion, where attendees will consider: • How can we synthesise all of this together and what are the next steps for creating a precision prevention pathway? • Who are the stakeholders and how should risk- and value-sharing be considered?
16.50 – 17.00	Final remarks from co-chairs

Annex II - Attendees

Chairs
Professor Katherine Payne, Professor of Health Economics, University of Manchester
Professor Sir John Tooke FMedSci, Professor of Medicine, University College London[17]

Speakers
Professor Barbara Casadei FMedSci, BHF Professor of Cardiovascular Medicine, University of Oxford
Professor Sir Mark Caulfield FMedSci, Chief Scientist, Genomics England
Professor Neil Hawkins, Professor of Health Economics & Health Technology Assessment, University of Glasgow
Professor Julia Hippisley-Cox, Professor of Clinical Epidemiology & General Practice, University of Oxford
Professor Mark Sculpher, Professor of Health Economics, University of York
Dr Stephen Williams, Chief Medical Officer, SomaLogic

Participants
Dr Saddif Ahmed, Clinical Product Manager, Babylon Health
Dr Nisreen Alwan, Associate Professor in Public Health for Medicine, University of Southampton
Dr Sue Bailey, Strategic Partnership and Early Asset Director, Bristol-Myers Squibb
Ms Nicki Bromwich, Chief Operating Officer, MedCity
Professor David Burn FMedSci, Pro-Vice Chancellor and Professor of Movement Disorders Neurology, University of Newcastle
Professor John Deanfield, British Heart Foundation Vandervell Professor of Cardiology, University College London
Professor Diana Eccles, Dean of Medicine, Professor of Cancer Genetics, University of Southampton
Professor Ruth Gilbert, Professor of Clinical Epidemiology, University College London
Dr Karen Griffiths, Strategic Delivery Manager, Leeds Academic Health Partnership
Dr Keith Grimes, Clinical Artificial Intelligence & Innovation Director, Babylon Health
Dr Jennifer Harris, Discovery and Research Policy Executive, Association of the British Pharmaceutical Industry
Dr David Hughes, Lecturer in Biostatistics, University of Liverpool
Professor Dame Anne Johnson FMedSci, Professor of Infectious Disease Epidemiology, University College London
Mr Ian Jones, Owner, Jinja Publishing
Dr Constantinos Kallis, Research Associate, Imperial College London
Professor Frank Kee, Director, UKCRC Centre of Excellence for Public Health Research (NI), Queen's University Belfast
Dr Louise Knowles, Acting Deputy Director of Research Faculty, Infrastructure and Growth, Department of Health and Social Care
Dr Melanie Lee CBE FMedSci, Chief Executive Officer, LifeArc
Mr Steve Lee, Director of Diagnostics Regulation, Association of British HealthTech Industries
Dr Jonathan Loukes, Associate Medical Director, Vertex Pharmaceuticals
Dr Andrew Mackenzie, Head of Policy and Communications, The Physiological Society

[17] Professor Sir John Tooke FMedSci is on the Medical Advisory Board of SomaLogic, who were invited to speak at the meeting.

Dr Maeva May, Head of Policy, British Heart Foundation
Professor Gil McVean FRS FMedSci, Chief Scientific Officer, Genomics plc
Mr Mark Messenbaugh, Senior Vice President, Global Market Development, SomaLogic
Ms Susan Mitchell, Head of Policy (Prevention, Early Detection and Diagnostics), Alzheimer's Research UK
Dr Omar Moreea, Technical Analyst, National Institute for Health and Care Excellence
Professor Andrew Morris FMedSci, Director, Health Data Research UK
Dr Séamus O'Neill, Chief Executive Officer, Northern Health Science Alliance
Mr Johan Ordish, Group Manager (Medical Device Software and Digital Health), Medicines and Healthcare products Regulatory Agency
Professor Nora Pashayan, Professor of Applied Cancer Research, University College London
Dr Laura Portas, Research Associate in Epidemiology and Medical Statistics, Imperial College London
Professor Rosalind Raine FMedSci, Professor of Health Care Evaluation, University College London
Dr Andrew Roddam, Chief Executive Officer, Early Disease Detection Research Project UK
Dr Gurdeep Sagoo, Lecturer in Health Economics, University of Leeds
Professor Stephen Senn FRSE, Consultant, Luxembourg Institute for Health
Professor Claire Shovlin, Professor of Practice (Clinical and Molecular Medicine), Imperial College London
Professor Ewout Steyerberg, Professor of Clinical Biostatistics and Medical Decision Making, University of Leiden
Dr Alex Thompson, Research Fellow, University of Manchester
Mr Thomas Walker, National Institute for Health and Care Excellence
Mr Ian Watson, Senior Technical Advisor - Methods, National Institute for Health and Care Excellence
Professor Tony Whetton, Director of the Stoller Biomarker Discovery Centre and the Manchester Precision Medicine Institute, University of Manchester
Professor Sarah Wordsworth, Professor of Health Economics, University of Oxford
Professor Christopher Yau, Professor of Artificial Intelligence, University of Manchester

Staff and secretariat

Dr James Squires, FORUM Policy Manager, Academy of Medical Sciences
Dr Emma Laycock, Policy Officer, Academy of Medical Sciences
Dr Claire Cope, Head of Policy, Academy of Medical Sciences
Mr Tom Langford, Policy Intern, Academy of Medical Sciences
Ms Helena Teague, Policy Intern, Academy of Medical Sciences
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