FAST HEALTHCARE NETWORKS PLUS

April 2020

Workshop on the Early Detection of Cancer

1 Introduction

The Workshop on the Early Detection of Cancer was the fifth workshop in a series organised by the EPSRC Fast Assessment and Treatment in Healthcare (FAST Healthcare) Networks*Plus* (www.fast-healthcare.org.uk). Held in Cambridge at Robinson College on 18th February 2020, the workshop was organised by Professor Andrew Flewitt (Engineering Department, Cambridge University) for the FAST Healthcare Networks*Plus*, in collaboration with the Early Detection team from Cancer Research UK (CRUK) and Dr Wendy Alderton from the CRUK Cambridge Centre. Its purpose was to provide a forum for participants from a variety of backgrounds to identify and discuss the clinical needs for technologies within three early detection research themes that have recently emerged from a multi-sector stakeholder consultation convened by Cancer Research UK. These were:

1) Analysis of electronic health records
2) Wearables and point of care
3) Digital twins

Participants then worked together to map the underlying research and technology development pathways required to address the clinical needs identified. Key challenges of developing and translating early detection technologies were also discussed, to enable researchers to anticipate these in advance and be more likely to succeed in developing a product suitable for clinical use. An important component of the workshop was to allow participants to identify opportunities to collaborate on future project proposals to address the research pathways identified.

This report, based on the workshop proceedings, aims to disseminate the findings from the workshop to a wider audience, providing clarity to researchers about where it would be worthwhile directing research, and where there is potential for collaboration. It includes an introduction to each research topic followed by an analysis of the research pathways identified to address clinical needs. Cross cutting themes that emerged regarding the development of new technologies and their translation into healthcare are also discussed.

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2 Background

Being able to detect and diagnose cancer earlier is important if we are to reduce cancer mortality rates and improve patient outcomes. Many cancers are most successfully treated when diagnosed earlier, leading to dramatic increases in five- and ten-year patient survival. For example, the relative ten-year survival rate of patients diagnosed with Stage I colorectal cancer is over 90%, compared to less than 5% for patients diagnosed with stage IV cancer (Figure 1). However, the most recent data available from 2014 suggests that almost half of all cancers are diagnosed at a late stage in England and Northern Ireland [1]. There is therefore a clear need for more research and development of technologies that are able to facilitate the earlier detection of cancer, whether that is improving on current screening programmes, or identifying novel biomarkers for risk stratification and diagnosis that could be incorporated into a point- of- care test. In addition, understanding the biology that underpins pre-cancerous and early disease can not only be used to develop early detection tools, but could also help reveal targets for better precision medicine and prevention strategies.

Early detection research seeks to enable the detection of consequential cancer, or pre-cancerous states, at the earliest possible time point at which an intervention might be made. This includes:

- Understanding the biology that underpins pre-cancer/early disease
- Discovery and validation of marker signatures which detect (and prognose/stratify)
- Developing technologies which will enable detection of robust, informative signals
- Translational and clinical research; proof of concept for new early detection approaches

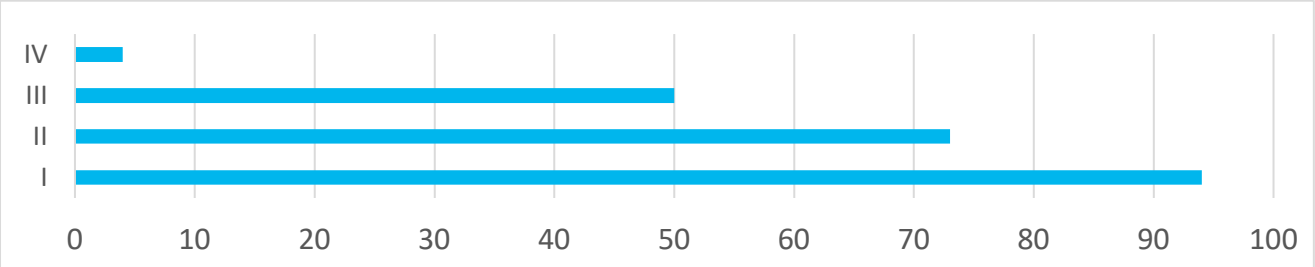

Figure 1: 10 year relative survival for colorectal cancers by stage of diagnosis (%) (Figure provided by CRUK)

Working in the field of cancer early detection presents several unique challenges, which have hampered progress in this area, but also provide opportunities for improvement. A key issue is the potential for overdiagnosis, which occurs when an individual is diagnosed with a cancer that if undetected would never have turned out to cause any harm. This can result in individuals receiving unnecessary treatment and experiencing associated psychological harms, and is a particular problem in population wide cancer screening programmes of mostly asymptomatic individuals. For example, in breast cancer screening it can be difficult to differentiate between lesions that are harmless (benign) and those that would develop into an aggressive cancer. In the UK, it has been estimated that 19% of women diagnosed with breast cancer though screening experience overdiagnosis, though this figure is uncertain as a result of limitations of the studies used to generate this estimate, including a lack of data and incomplete follow up of women diagnosed [2]. Work is currently ongoing to more accurately estimate overdiagnosis in breast cancer, to inform future use of mammography [3]. Therefore, reducing overdiagnosis is important in improving the success of screening and other early detection interventions. Ways to do this include focussing risk-stratification on identifying who in the population would most benefit from early detection and diagnosis. Consequently, by targeting the right groups of people, it should be possible to reduce burden on the health system (including cost) and reduce unnecessary anxiety for individuals.

Other challenges to early detection research include the complexity of cancer biology and the resulting technology requirements, which often must be extremely sensitive and specific for effective early stage cancer detection. Since research efforts have tended to focus on later stage treatment there has been less work in this area overall, with a lack of

prioritisation in research and industry and a lack of visibility for early detection research. To develop innovative solutions, expertise is often required from different disciplines including engineering and biology, and this exchange of knowledge is often lacking.

In the workshop participants aimed to identify research workflows that could help provide solutions to these challenges to allow interventions to be designed to meet clinical needs. The three overlapping topics of the workshop were selected as key areas for early detection research and will be described further in each of the following chapters.

3 Methods

The Workshop involved participants from academia, including those with an interest in digital medicine in various areas of the health sector, data science and engineering science, health services and the commercial sector.

There were three sessions covering different areas of work in early detection, each taking the form of one or more presentations introducing and providing examples of research in an area, followed by division of the participants into three or more discussion groups. The aim of the discussion groups was to populate planning sheets with ideas for clinical drivers within each topic discussed, the enabling engineering underpinning the solution to the driver, and the fundamental technology required. Participants were encouraged to make links between these different areas.

The sessions covered three main areas of early detection technologies:

1. Analysis of electronic health records
2. Wearables and point of care tests
3. Digital health twins

The report has been developed using:

- Material from the presentations which provided an introduction to each topic
- Information from each of the individual group planning sheets, to illustrate the key research pathways and requirements identified for each of the three different early detection areas
- Material from presentations, planning sheets and group discussions, which have been used to identify cross-cutting themes for research and technology development in the field of cancer early detection

4 Analysis of Electronic Health Records

Introduction

In this session the use of electronic health records (EHRs) in cancer research and early detection was discussed. A patient's electronic health record refers to the digital format of the information collected during their encounters with the health service, which was traditionally stored on paper. Here, two examples were provided of clinical scenarios in which health informatics analysis of the information stored in electronic health records could be used to improve early diagnosis. The first example concerned use of electronic health records when developing population risk stratification models based on computer algorithms using statistical modelling, machine learning or other methods. It was presented by Dr Adam Brentnall, who is a Senior Statistician in the Centre for Cancer Prevention at Queen Mary University of London. His research interests are focussed on the statistical design and analysis of cancer prevention studies, and methodological issues that arise therein. The second example discussed use of electronic health records as a decision support tool in primary care, and was presented by Professor Brendan Delaney, who is Professor of Medical informatics and Decision Making in the Institute for Global Health at Imperial College London. His research encompasses artificial intelligence, cancer diagnosis and learning systems, eSource for clinical trials and global eHealth.

Example 1: Artificial intelligence based risk stratification models for asymptomatic patients or patients with vague symptoms

Early stage cancer patients are often asymptomatic or have vague symptoms that make cancer diagnosis very difficult. This has led to the development of nationwide screening programmes or individual screening tests for some of the most common cancers, to increase the rate of early detection in cancers that would otherwise probably only be detected at a late stage. The UK has national screening programmes for breast cancer, bowel cancer and cervical cancer. There are also early detection tests that have been developed but which are not recommended on a population, such as the prostate specific antigen (PSA) biomarker test for prostate cancer.

Screening is the systematic application of a test to identify individuals at sufficient risk of disease who will benefit from further investigations to diagnose the disease. It occurs in

patients who are asymptomatic. A number of criteria need to be satisfied for a screening test to be recommended by health systems. A blueprint of these was set out in 1968 in a report for the World Health Organisation by Wilson and Jungner [4]. These criteria apply more generally to early detection tests, which are not necessarily carried out systematically.

One of the Wilson criteria is that the benefits of the test outweigh the harms. Benefits from early detection of disease arise when the effect of treatment on prognosis at an earlier stage of disease is better than at a late stage. Potential harms from early detection include those due to the further investigations to diagnose the disease in those who do not have disease. It is important that harms from the subsequent interventions due to testing positive do not outweigh the benefits arising in those whose disease is detected early (see Table 1).

Table 1: Impact of false positives and false negatives in breast cancer screening

Test result	What does this result mean?	Impact on the subject
True positive	The subject **does** have breast cancer, and the screening test identifies this. The subject will go on to have further tests to confirm the result and diagnose the type of cancer.	The subject receives treatment for the cancer earlier than they would have if it had not been detected by screening. This could have a significant impact on patient survival and quality of life, especially if the cancer is early stage.
True negative	The subject **does not** have breast cancer, and the test does not indicate that the subject has a breast cancer. No further action is required.	The subject is reassured that they do not have cancer and no unnecessary treatment is carried out.
False positive	The subject **does not** have a breast cancer, however the screeing test appears abnormal and requires further investigation.	The subject may be caused unnecessary anxiety. Further tests needed to verify the cancer isn't there can cause Pain, bleeding and infection and take time.
False negative	The subject **does** have breast cancer, however it is not detected and further tests are not carried out until the subsequent screening interval.	An opportunity for early detection has been missed. The subject is given a false sense of security, thinking they do not have cancer when actually they do. If the cancer progresses before it is detected then prognosis will be significantly worse than if the cancer was detected and treated at an early stage.

The PSA test an example of a screening test that is likely to reduce mortality, but is not recommended as part of national screening programmes due to associated harms arising. These include overdiagnosis and overtreatment of slow-progressing prostate cancer.

One way to improve the benefit to harm ratio associated with an early detection test is to use it in patients at higher risk of a disease, or higher risk of aggressive disease. If the characteristics of the test (detection rate and specificity) remain constant, then applying the test in a higher-risk populationwill provide a greater positive predictive value of the test and the population who receive the test will have a better benefit-to-harm profile.

An illustration of how screening a population at increased risk for a rare cancer could improve the positive predictive value of a test (the probability that individuals with a positive screening test actually have the disease) is given in Figure 2.

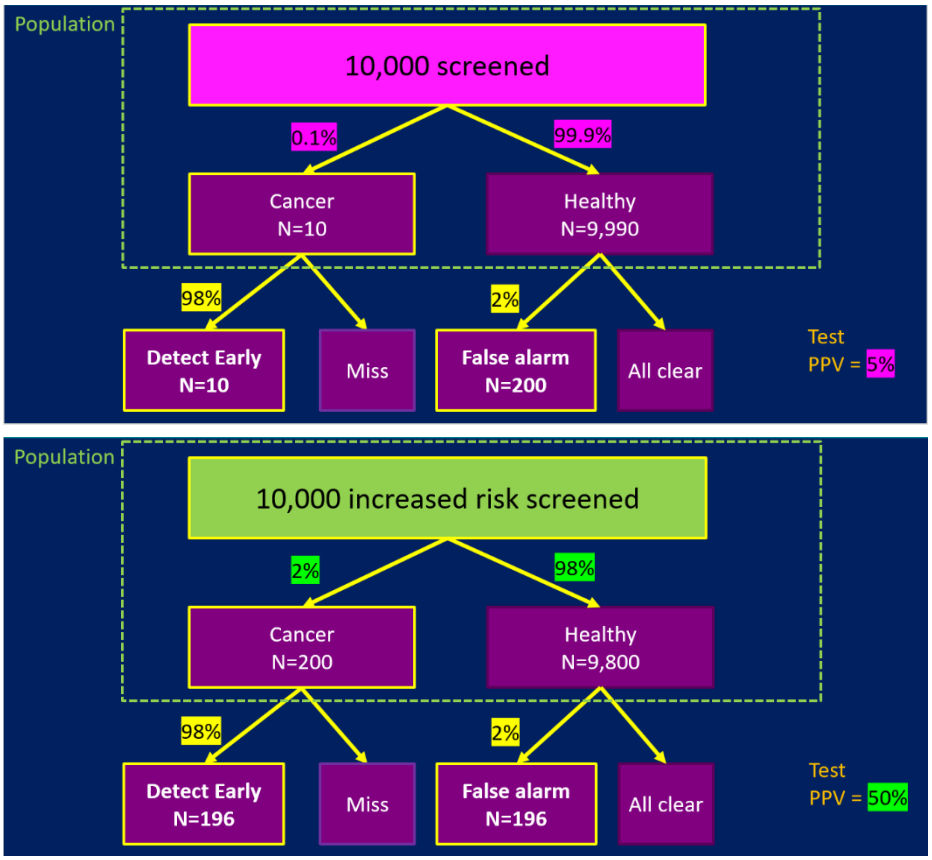

Figure 2: Identifying a higher risk population for screening can improve the positive predictive value of a test [provided by Dr Adam Brentnall, Queen Mary University of London]. Use of the same test for a rare cancer, which has a sensitivity and specificity of 98%, will have a higher positive predictive value if used in a population whose likelihood of the cancer is 2%, than if used in a population whose risk of cancer is 0.1%.

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One approach to target early detection tests to those who will benefit the most is to use risk stratification models. These may be developed in different ways. One approach requires large patient data sets linking clinical data to outcomes, which can be analysed using tools including statistical models and machine learning to identify those at highest risk. Data for such analysis might be sourced from large studies such as the UK Biobank, or from routine data such as from electronic health records. As a model is only as good as the data it is derived from, both approaches have their advantages and disadvantages. For instance, the variety of people who use healthcare systems (such as visit their GP) are more likely to be representative of the country as a whole than those who enrol in a large-scale study. However electronic health records currently suffer from drawbacks such as missing data entries, and incomplete data collection. In future if data is more routinely collected and stored, electronic health records may be used to develop better and more representative risk tools for stratification.

Example 2: Decision support tools in general practice

Most potential cancer cases will first be encountered when a patient visits a GP surgery, making this a key opportunity for early diagnosis (Figure 3). However, whilst it is known that early diagnosis of cancer improves outcomes, there are many reasons why it is currently difficult to diagnose cancer early. One is that symptoms of many cancers are non-specific and often only become apparent once the cancer has reached a late stage. Individual beliefs of the patient can also lead them to consider that their symptoms are not serious or that they would be wasting the GP's time by discussing them. In addition, elderly patients in particular may have multiple comorbidities that mask the symptoms of a developing cancer. Symptoms of cancer may also be misinterpreted due to unconscious bias on the part of a clinician, or because the clinician's personal experience and interpretation of the knowledge available does not prompt them to consider cancer as a likely diagnosis. Finally, even when a cancer is suspected, features of the health system

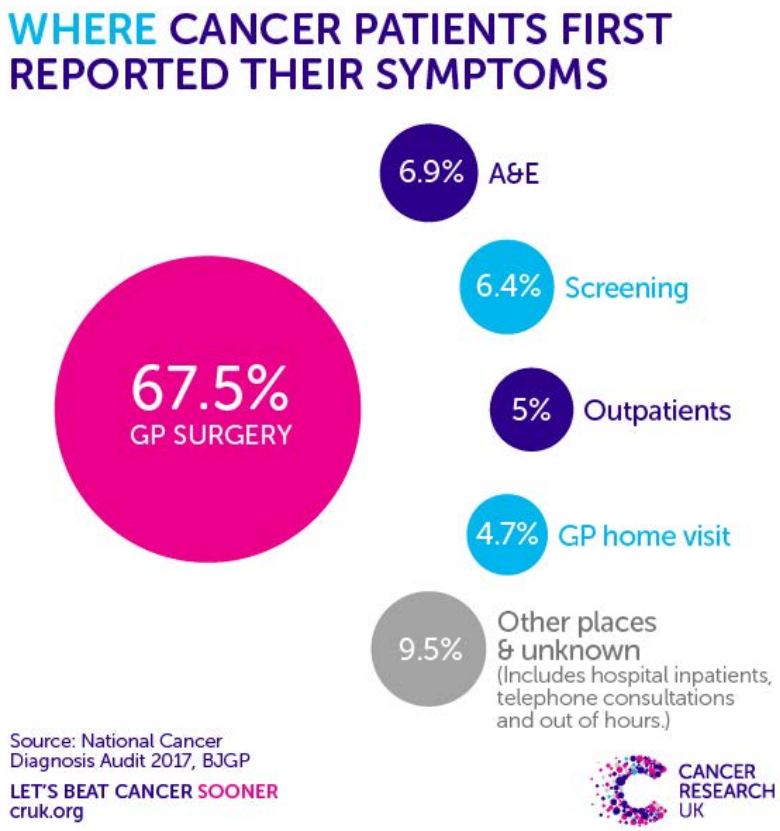

Figure 3: Where cancer patients first report their symptoms

such as delays in referrals to specialists and barriers to investigation from a lack of resources, mean that it can take a long time to make an official diagnosis and start treatment. GPs were asked about the causes of avoidable delays as part of Cancer Research UK's 2017 National Cancer Diagnosis audit of 17,042 newly diagnosed patients from 439 practices [5]. The top three causes identified were health professionals missing symptoms, delays in hospital care, and the individual beliefs of patients themselves.

Current strategies to help overcome these issues in UK primary care are based on support tools that can help estimate risk based on symptoms entered into electronic health records. For example, the QCancer algorithm is a risk score tool based on symptoms entered in previous and current GP visits, which is available on a GP's computer screen during a consultation with a patient [6]. The tool provides no assistance other than to provide a long list of potential symptoms to check, and as it still relies on a GP entering these symptoms in the first place, may still be prone to bias. There is therefore a need for a decision support tool (or tools) which is integrated with electronic health records, and produces information relevant to the diagnostic decision being made at the time of use. The tool would require the use of algorithms derived from unbiased data, and should be capable of supporting audits. It would be important that such a tool be a certified medical device, which is able to learn and improve over time.

It is well known that people can formulate hypotheses very quickly in new situations which then impact all subsequent decision-making in a disproportionate matter. In the context of cancer this can mean that unless a cancer diagnosis is considered by a clinician from the start of an appointment, they may be less likely to go on to consider cancer as a potential diagnosis. To overcome this problem, a prototype device has been designed which can be incorporated into an electronic health record system. The device is able to present clinicians with a differential diagnosis list at the start of an appointment, based on the reasons for a patient's visit. After reading the list, the clinician can then start the consultation with the patient. In addition, the tool is able to form part of a learning health system, where the results of the consultation feed back into the electronic health record to inform future performance.

When this tool was tested in a simulation with 34 GPs consulting with 12 standardised patient actors, there were significant improvements in diagnostic accuracy, without significantly affecting the number of tests ordered, length of consultation or patient

satisfaction. In addition, the data being entered into the electronic health record system with use of the tool was found to be much less biased than that being entered into the system with use of electronic health records alone. The researchers now aim to take their European prototype into a feasibility study in 40 GP practices, and perform an in-depth real-world study in five practices.

EPS Research Roadmap

Figure 4 shows the Workshop's Roadmap for Engineering and Physical Sciences (EPS) Research interventions in the area of analysis of Electronic Health Records (EHRs). It is built around three key clinical drivers. The first of these is the need for timely and accurate risk stratification if early detection is to be effective, as discussed above. Associated with this is the need to use phenotyping to identify people with similar risk profiles; this will assist in improved risk stratification. An associated clinical driver which sits alongside early detection is the need to identify the optimum window for clinical intervention, which is critical to determine which cancers will go on to be consequential.

Two EPS research intervention pathways are identified which lead to addressing these clinical drivers. The first of these is around the need for quality patient-specific models, which then leads to improved risk score calculations and associated ways of presenting the resulting information in a helpful way to clinicians to support decision-making. It is noted that Digital Twins may have an important role to play in this regard (see Section 6). The second pathway sees daily activity data (which may come from wearables as discussed in Section 5) together with environmental data coupled with means of cleaning and standardising existing EHR data and protocols for sharing and integrating data. This would allow rich longitudinal data analysis leading to the clinical drivers described. It is noted that identification of data gaps is important to avoid false conclusions to be drawn.

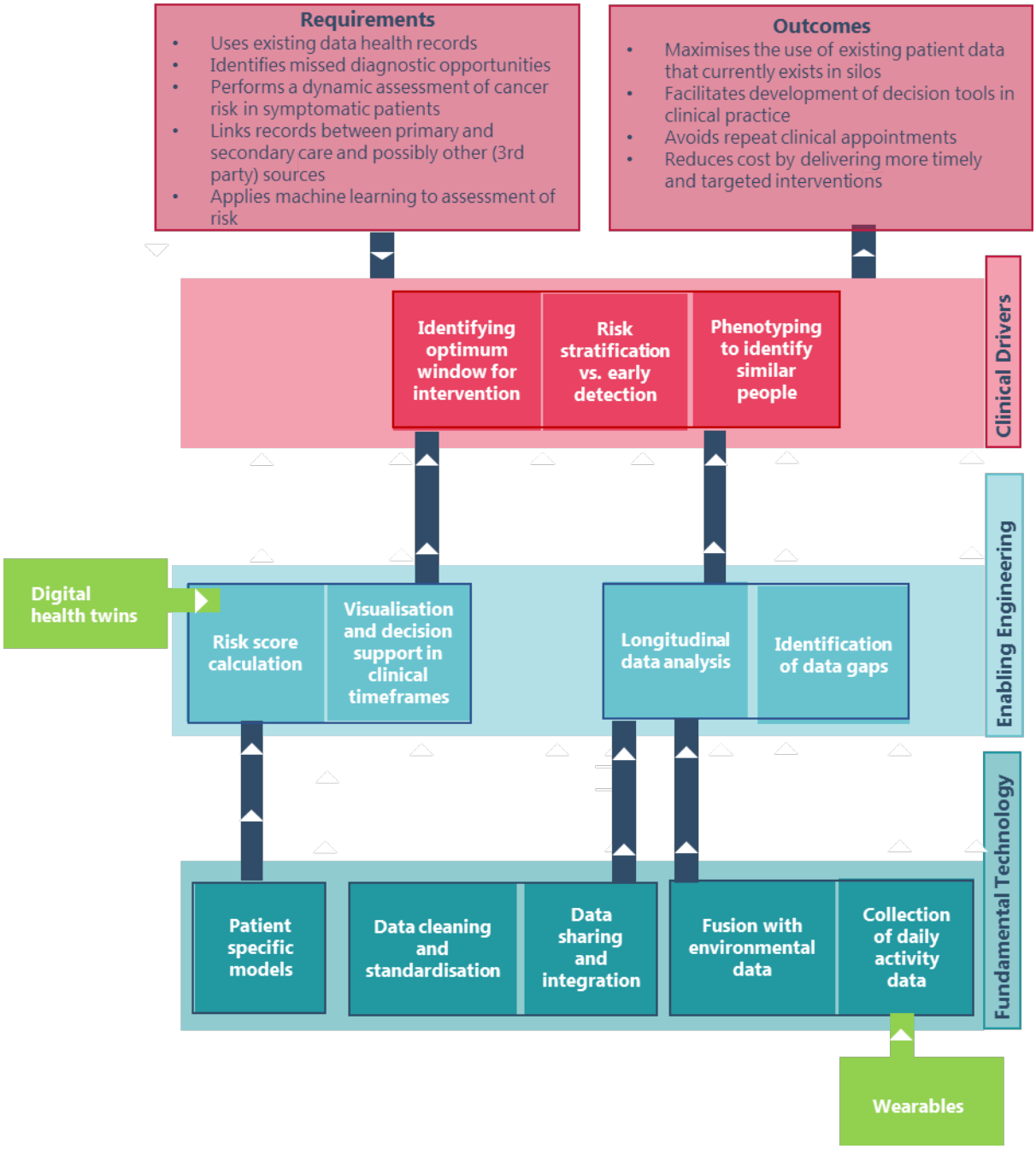

Figure 4: Roadmap for EPS research interventions addressing analysis of EHRs for early detection.

5 Wearables and Point of Care devices

Introduction

The aim of this session was to illustrate general considerations when developing wearables and point of care devices, with specific examples of how these devices can have an impact on early detection.

Point of care testing

Point of care testing (POCT) refers to the use of tests that are carried out at the time and place of initial contact/care to deliver rapid results. This offers immediate benefit to patients through reducing anxiety and the inconvenience needed to make a separate appointment to receive results. It can also provide lower costs to the health system from not having to send off samples, and reduce time pressure on clinicians through the reduced need for multiple appointments. Point of care testing can also improve the likelihood of detecting cancer early though increasing the uptake and use of diagnostic testing, as there may be a much lower barrier to carrying out the test if it is faster and can provide clear results to enable decision making. This also means that testing can be carried out more readily to provide longitudinal data, which can be useful in identifying long term trends that would indicate a developing medical condition. It should be noted that not every cancer diagnosis will require a point of care test and that even if used, it would only form one step in a medical diagnostic pathway; the presence of cancer is confirmed via biopsy and histology.

There are several requirements for a successful point of care test, which should be kept in mind when planning to develop a new point of care test.

- As tests are likely to be used within a GP appointment, often by a clinician rather than a scientist, it must be possible to administer the test easily and quickly (within the period of a normal consultation). In order to ensure the test is user friendly it is essential to engage the end user early on in test design (e.g. GP or nurse).
- It must be possible to reliably extract the sample required for the test (e.g. the state of cleanliness of a patient's finger for a finger prick test may influence the test result). To be useful the test must be consistent, reliable and simple.

- The clinician has to be confident in the result of the test – if there is a better test that takes longer in terms of returning results the clinician would likely choose that test. An important component of confidence is that the clinician must be able to understand the data produced.
- The clinician has to be able to act on the test result, therefore it is important to consider when and where the test will be used in the clinical pathway.
- The test must be economically viable which includes considering the cost per unit of the test, how frequently the test is used, what resources are required to deliver it, and the upfront cost of equipment needed. For example, it is preferable for tests to use generic equipment present in a GP surgery, otherwise surgeries would have high upfront costs for each new test required. As the incidence of cancer may be very low in any one GP practice, generic equipment is likely to be more economically viable.

An example of how research can be used to develop a point of care test was given in the context of prostate-specific antigen (PSA) testing for prostate cancer by Professor Andrew Flewitt who is Professor of Electronic Engineering in the Engineering Department at Cambridge University. His research includes the development of microelectromechanical sensors including medical applications. In this example he identified a 'technology push' related to the development of a technology that had very high sensitivity for detecting the attachment of small quantities of specific biological molecules to a functionalised surface. A clinical need was then identified where this technology could be useful: the reliability of the PSA test for prostate cancer could be significantly improved by identifying the three different forms of the PSA protein [7]. The current PSA test is known to be unreliable as several factors can influence the total concentration of PSA in the blood, not just prostate cancer. However, it has been clinically proven that measuring the concentration of three different forms of the PSA molecule leads to accurate detection of prostate cancer and can even assess aggressiveness of the cancer . However, as this test measures three targets, it is more expensive than the total PSA test, and so has not been widely adopted. The challenge was then to enable uptake by both reducing cost and incorporating this technology into a point of care test.

Example 2: Wearable devices

Wearable devices are technologies that are worn on the body, such as Fitbit and Whoop, to constantly measure parameters ranging from simple functions such as heart rate and activity levels, to more clinical parameters such as blood glucose levels using implanted monitors worn by patients with diabetes. The value of these devices is not so much in their measuring capabilities, but more due to the analysis of these measurements producing useful and actionable results. The resulting information can be communicated instantly to the wearer and could result in them modifying their behaviour, or could potentially be used to communicate information to researchers or the healthcare system. Current technologies are relatively basic, but it is not necessary to develop wearables that are extremely complex in order for the data they collect to add value to healthcare. A current example is the EPSRC SPHERE project in Bristol, where the researchers have taken currently available environmental and non-medical sensors and placed them in the home, to learn more about the well-being of people based on their home environment [8].

In future it is anticipated that we will live with a network of small devices, integrated into items such as clothing and jewellery that will be able to continue to monitor physiological functions. It should be possible to obtain longitudinal data to monitor our health that can be used to detect changes to our well-being, including those associated with the potential onset of cancer.

There are several challenges associated with developing and using wearable technologies. Firstly, there is a need to make sense of data whilst respecting the privacy of individuals. It will be necessary for the need for privacy to coincide with requirements for data analytics, which will present fundamental engineering challenges (e.g. designing systems that only pass the minimum required data to the cloud for processing with preservation of anonymity). Another challenge for wearables is to ensure that they are used and used correctly, and consideration is needed on the best way to incentivise this. It will be necessary to take a systems engineering approach to bring all stakeholders together to produce a successful device, including medical professionals, patients, manufacturers and the healthcare system.

Key points to consider for the development of all medical devices:

For both point of care tests and wearable devices, several key points are applicable when considering their development:

- It is important to consider the real-world context in which a device is going to be used. How will the device and the results it produces sit within the traditional patient/clinician pathway?

- It is important to engage with stakeholders early on to understand the key requirements that the device has to fulfil.

- The upfront cost of the technology is a key factor that will affect its uptake. There is no point in investing in expensive new technologies if older ones already exist and can be harnessed in new ways.

- The device must be able to deliver a clinically actionable result.

- There is the potential for wearables to exacerbate inequalities and end user engagement at an early stage in the design process is therefore essential.

- It is also possible that wearables can cause unnecessary anxiety for the 'worried well', and therefore it is important to consider how information is presented to users and integrated with other data sources.

EPS Research Roadmap

Figure 5 shows the Workshop's Roadmap for Engineering and Physical Sciences (EPS) Research interventions in the area of wearables and POCT. The starting point is the aim to improve the awareness of both patients and GPs to early symptoms of cancer. There is also the possibility of encouraging lifestyle changes which may reduce cancer risk. For this to happen, we need to provide better information to both patients and GPs to enable them to make decisions. Underpinning this are the associated clinical drivers of having timely clinical appointments and good predictive accuracy based on POCT and wearable

data. There is also a strong link here to the roadmap for analysis of EHRs, as indicated in Figure 4.

Managing data clearly plays a central role in addressing these clinical drivers. Part of this relates to data handling, and in particular the need for open health data platforms, with secure upload interfaces and a quality assurance (QA) system for validating data. Feeding into this is the opportunity that wearables and POCT offer to gain longitudinal data (over a period of time), but this type of data is inherently complex and highly variable, and so means of managing this are required.

Underpinning all of this are the basic wearable and POCT devices which collect data in the first place. The 'Internet of Things' provides an opportunity to embed into healthcare sensors which interact with patients in their everyday lives, collecting data with minimal invasiveness. There are also opportunities for GP surgery-based tests which might make use of the time a patient is waiting to be seen by a clinician. In addition, emerging opportunities were identified for skin and breath analysis, and for voice and facial recognition; these could all be used over an extended period of time to identify changes in an individual's general wellbeing.

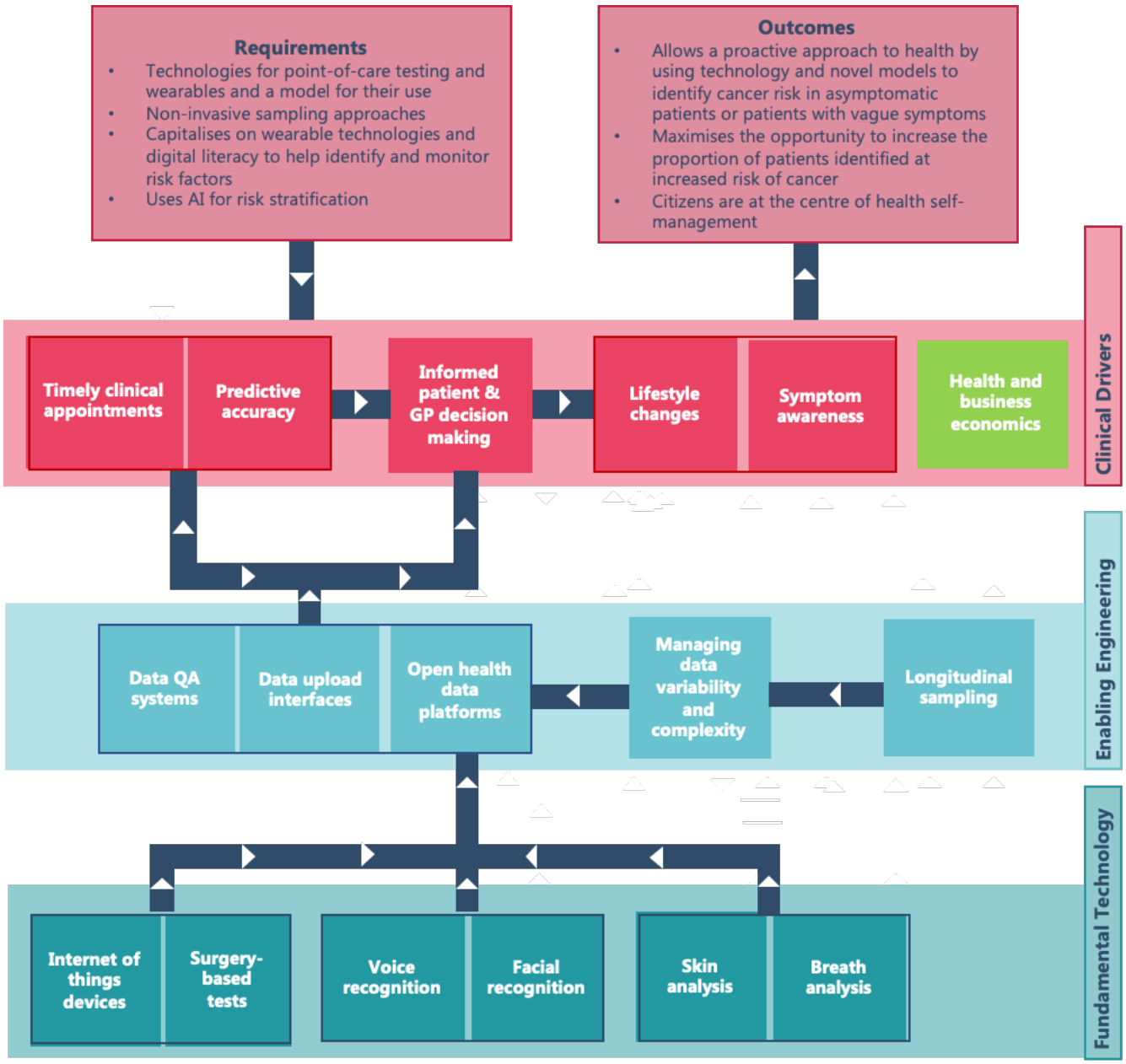

Figure 5: Roadmap for EPS research interventions addressing wearable and POCT for early detection.

6 Digital Health Twins

Introduction

In this session the concept of the digital health twin was introduced, alongside the underlying technology considerations. The example given of the application of digital twins in healthcare was in relation to vascular disease rather than cancer early detection, as the use of digital twins is particularly advanced in this field. However, the underlying concepts of digital twins could then be applied in relation to cancer. This was presented by Professor Vanessa Diaz, who is Professor of Healthcare Engineering in the Mechanical Engineering Department at University College London. Her research focusses on 'Multiscale Cardiovascular Engineering' to apply mathematical tools and engineering principles to understand cardiovascular pathophysiology for patients' benefit in what is called 'patient-specific modelling'.

A digital health twin can be thought of as a virtual physiological copy of a human patient, created by collecting and storing their entire health history. For example, this could include inputting their disease risks, symptoms, diagnostic test and examination results, medications, intervention history, and other data into a digital storage system. This information can then be used to create simulations to trial different potential interventions to select the most effective one for the patient without the need for multiple tests in real life. This means that fewer resources can be used whilst enabling precision medicine by best matching interventions to the specific patient. In addition, the model could be used to flag up risks and alert healthcare systems in advance.

Example: Digital Health Twins in Vascular surgery

Digital health twins are currently being developed at UCL to assist with aortic dissection management. Currently if a patient arrives in hospital with symptoms of heart disease their medical history is typically in the format of a collection of paper records, often outdated and with missing data. This is of limited use when making decisions about how to manage the patient. In addition, a variety of tests and scans are then needed to diagnose their condition and understand if they have an aortic dissection; this is a tear in the wall of the aorta, the major artery carrying blood from the heart. If the patient does have an aortic dissection the considerations surrounding the best way to treat it are extremely complex,

as no two dissections are clinically alike. The test results alone provide little assistance in helping to understand which type of treatment is the most suitable for the patient. Often patients determined not to need immediate surgery are discharged without any continuous monitoring to see if their condition stabilises or requires a stent. If patients do require a stent at a later date, it is difficult to determine the best way to place this and patients often have to return for repeat surgery.

A digital twin of a patient would overcome the problem of incomplete paper health records and be complete with updated scans, updated blood test results and updated monitoring tests. Upon arrival at the hospital, the scans showing an aortic dissection would also become part of the library of the digital patient. The combination of this information can be used to create a digital simulation of the patient, upon which multiple different treatment scenarios can be performed by the clinician. If the patient is discharged they can then continue to be remotely monitored and the information uploaded to the digital twin, so that if surgery is required this can also be simulated in advance to determine the best surgical approach and when it might be required.

The current model for aortic dissection being developed by UCL uses simulations based on the patient's *in vivo* data results, and physical testing using a 3D printed model of the aortic dissection. The physical model is valuable for simulating conditions influencing the success of surgery, such as pressure and flow inside the lumen, which could otherwise not be measured non-invasively. The model can also be used to trial surgical interventions. The aim of this process is to develop computational tools to be able to specifically measure each patient's blood flow based on the physical model and the routine clinical data collected. These computed blood flow models could then be compared against real-life measurements to test their accuracy, and ultimately be used by surgeons to simulate surgical interventions in advance of surgery.

In this scenario a combination of both machine learning and mechanistic modelling was used based on the digital twin, with each method considered to complement the other. It was cautioned that though machine learning can be useful, the ability of machine learning to make useful predictions depends on the quality of the data sets it is based upon. The current amount of data that is collected in healthcare may not have the required complexity to develop machine learning models. In contrast, there remains the ability to

make physical mechanistic models which can be used to perform tests and generate real measurements, and the utility of this should not be underestimated.

In addition to being useful for planning surgery, several other uses have been identified for the digital twins and their associated 3D models. These include empowering patients by helping them to understand their condition or the repercussions of an intervention. For example, the 3D models could be used as part of a patient-doctor conversation to help patient understanding. The physical platform could also be used for testing of medical devices to mimic *in vivo* conditions, minimising the need for animal experiments, as well as be used to help develop new medical devices. In addition, tools could improve understanding of the development of other vascular related diseases, such as plaque formation in specific patients and the role of the peripheral microcirculation in diabetic patients.

A potential challenge raised during workshop discussion for the use of digital twin models was their regulation, including how to perform clinical trials to gather evidence of their effectiveness. As interventions become more personalised it will become increasingly difficult to carry out traditional large randomised controlled trials to provide evidence. The US Food and Drug Administration (FDA) is currently considering how to regulate new AI strategies, and the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK will also need to develop new regulation if new personalised technologies that belong to high risk categories are to be developed.

EPS Research Roadmap

Figure 6 shows the Workshop's Roadmap for EPS Research in the area of digital twins applied to early detection of cancer. Specific clinical drivers for development of digital twins were identified as the ability to create virtualised care pathways and health system simulations that can be applied to individuals; this addresses an underlying theme running through this Workshop that early detection of cancer is only helpful if it is both actionable and applicable to the individual patient, otherwise the result is clinically meaningless and/or can potentially lead to overdiagnosis/overtreatment. Digital twins also offer the prospect of being able to identify individuals who need to see a clinician (see also the reference to timely clinical appointments in the Wearable and POCT roadmap shown in Figure 5) and cost-effective, actionable interventions. Together, addressing all of these

clinical drivers could also help to ensure equality of access to early detection regardless of an individual's background, which is a broader objective that digital health technologies are trying to address. Running alongside these clinical drivers is the need for probabilistic health economic models of early detection interventions which are essential for ensuring cost-effectiveness.

The enabling engineering that sits behind these clinical drivers is focussed around the development of high-quality models for ageing in general (so that deviation from an expected wellbeing trajectory can be identified), models for cancer and precancerous conditions and models for clinical interventions to understand the effectiveness of specific interventions in the context of broader care pathways. Finally, these models must be underpinned by accurate profiling of individuals based on biomarkers, behaviour, genetic information and imaging data, coupled with statistical models for risk trajectories.

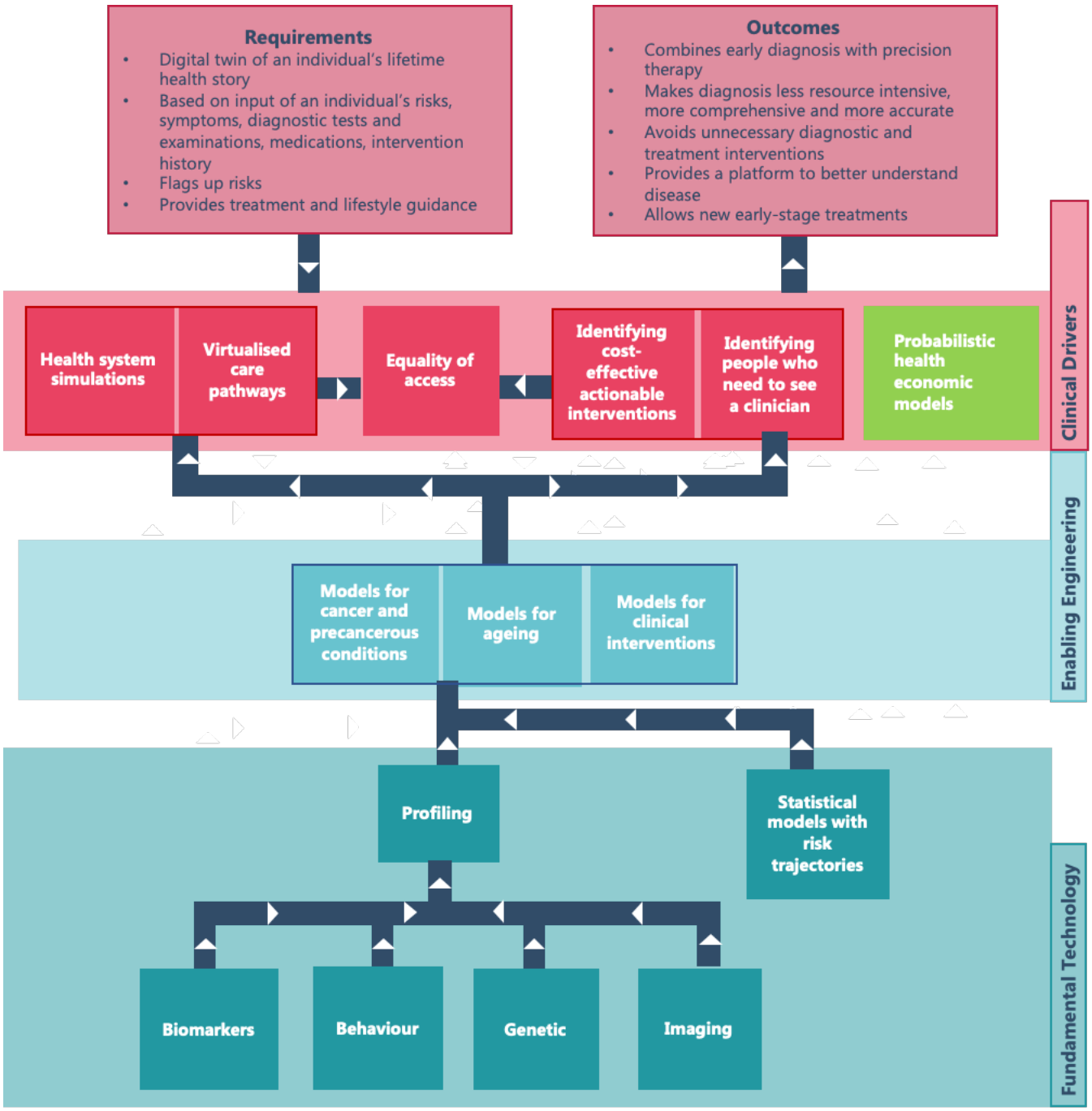

Figure 6: Roadmap for EPS research interventions addressing wearable and POCT for early detection.

7 Cross cutting themes

Throughout all the different sessions and from conversations between workshop participants, several cross-cutting themes were identified that applied to research, development and commercialisation of new technologies across the field of early detection. The main themes identified are summarised here.

Underlying research and technology

- **Access to longitudinal data**
  Development and identification of new technologies for early detection often requires large longitudinal data sets, especially if machine learning is to be used. There are concerns over firstly whether these data sets exist, and secondly how to access these data and the potential cost implications to research, especially when beginning a research project. There is also a requirement for longitudinal data sets which begin when a patient is still classified as 'healthy'. The new UKRI-supported Accelerating Detection of Disease (ADD) cohort may help provide answers to this problem.

- **A need for quality, real-world data**
  The point was frequently made that output of algorithms is only as good as the data input. There is a recognised need for real-world data such as that from electronic health records that could be used to validate or even replace data from potentially biased studies. However, the data entered into electronic health records is often inconsistent and requires cleaning, a process which could limit its large-scale use in healthcare.

- **Data protections, privacy and identification issues**
  When carrying out research there is a need to collect and link data from different data sets whilst protecting patient privacy. This is a technological challenge in its own right but also an ethical question over how data should best be stored and used.

- **Difficulties obtaining funding for 'blue skies' research**
  In order to identify entirely new connections between previously unidentified symptoms and the onset of cancer, using tools such as machine learning, funding may be required based on little previous evidence being available. This can be difficult to obtain.

- **Regulation of wearables**
  It was recognised that if data from wearables is to be used to inform healthcare, then these wearables need to be regulated in order to ensure that the data produced is of consistently high quality.

- **Regulation surrounding highly personalised technologies**
  There is an ongoing challenge surrounding the clinical validation of technologies that are highly personalised to the patient, as it is much harder to recruit enough patients to the large randomised studies currently used to generate evidence. In future regulatory changes will be needed if these technologies are to continue to be developed.

Making a viable test suitable for use in the clinic

- **Positive health impact**
  New diagnostic tests must be useful beyond the current standard of care, with sufficient diagnostic accuracy for their intended purpose. It is not enough just to make a test, it must be able to inform clinical decision making to improve health outcomes.

- **Sufficient uptake**
  A test must be affordable, accessible and acceptable enough for the intended end user, whether that is a health care system or an individual. For example, lung cancer screening has been available in the US for five years but people do not take the test

(reference). In this scenario it may be better to compromise on performance, if a worse performing test still meets minimum requirements and has better uptake.

- **Viable business model**

  In order to be developed further for clinical use a test typically has to be profitable. This means it must be able to sustain a competitive advantage against other tests, and capture a large enough market size. As discussed earlier, costs for diagnostic tests must be kept low to be implemented for population-level screening, which is often not an appealing business model.

- **User engagement**

  As with all healthcare technology developments, it is essential to engage with users, including patients and the general public, to ensure that products are eventually successful. There are many patient specific patient groups who can act as a conduit for such efforts. Engagement with GPs and other clinicians more widely is also important.

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8 References

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