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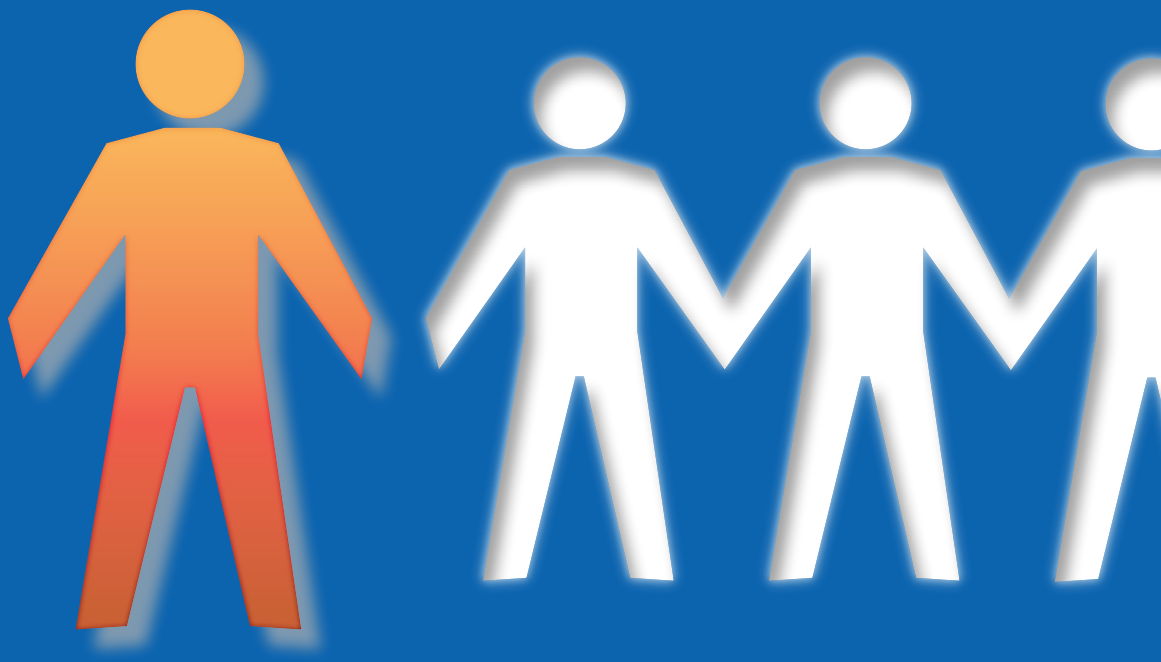
The personalised medicine technology landscape



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Foreword

Professor Dame Sue Hill, Chief Scientific Officer for England

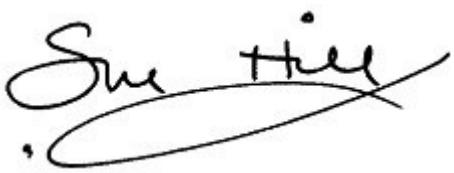
Within the next decade we will see an evolution in medicine as we understand more about the underlying drivers of a patient's condition and their individual response. We are starting to look beyond a 'one size fits all' approach to presenting symptoms to build a clearer picture of the many factors driving each individual's health and how they will respond to intervention.

This evolution to personalisation in medicine is not new, but is being driven by scientific advances and the development of new technologies, particularly the huge leaps in computing power that have driven the development of artificial intelligence and data analytics. Innovations such as 3D printing and circulating tumour DNA analysis are also providing ways of personalising care as never before.

The integrated structures of the NHS put us in a unique position to realise the potential benefits including earlier diagnosis, increasing treatment possibilities by identifying disease earlier; greater diagnostic yield and more precise diagnosis, allowing the potential for better segmentation of conditions with increased treatment effectiveness through better treatment selection.

NHS England set out its vision in *Improving Outcomes through Personalised Medicine* in 2015 and, through the development of the NHS Genomic Medicine Service, is starting on a journey to put in place the infrastructure to support the implementation of emerging technologies in the future. The pace of change in this field is significant, so it is essential that the service is able to respond to future changes and maintain our world-leading position in the use of these technologies.

The opportunity and the potential is in no doubt – the ability to deliver a win-win of improved outcomes and patient experience & participation while improving the efficiency of our precious health service resource. This evidence synthesis by the respected policy analysts at the PHG Foundation provides important insights as to how to take this vision forward and the issues we will face in implementation. This report will be valuable for everyone across the service who is working to achieve that goal.



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Executive summary

As the National Health Service (NHS) marks its 70th anniversary it can boast a rich history of innovation. Over the years scientific and technological advances have transformed medical practice and ongoing innovation across biomedical, digital, computer science and engineering disciplines continue to offer novel approaches to improve patient care. More recently the convergence of technologies such as genomics and informatics is presenting significant opportunities to drive improvements through more personalised treatment and care of patients.

In recognition of these opportunities, NHS England has set out its vision for personalised medicine and how it intends to build on the work undertaken as part of the 100,000 Genomes Project. More broadly there is growing emphasis on the need for improvement in the effectiveness with which the NHS fosters innovation and delivers it to patients, in order to improve outcomes, to support the national economic interest and ultimately to ensure the long term sustainability of the NHS.

Executive summary

Objectives and approach

This review presents an independent evidence synthesis to inform the NHS as it seeks to develop its approach and policies to support the delivery of personalised medicine and realise its benefits for patients. To align with the timescales of the Five Year Forward View – a wide-ranging strategy for the NHS in England – this review predominantly focuses on the near-term opportunities and associated challenges, and briefly reflects on the longer term perspective on how developments in technology and knowledge could enable a whole system transformation and advance personalised medicine.

This evidence synthesis, informed through a process of desk-based research and analysis of public sources of information, grey literature, and peer-reviewed publications, along with interviews with relevant experts and stakeholders, sets out to:

- Review developments in biomedical and digital technologies that have been proposed to contribute to the personalisation of medicine
- Identify and describe specific examples that have a sufficiently well-developed evidence base for validity and utility such that they would be able to underpin the delivery of personalised medicine in the next three years
- Analyse how some of these approaches could be integrated most effectively within the NHS and highlight key considerations for action that NHS England could take to develop and deliver personalised medicine

The road to greater personalised medicine in the NHS

Genomic information is an important component of personalised medicine, helping to inform and refine the diagnosis, treatment and prevention of disease. A National Genomic Medicine Service, to be operationalised in 2018, will form the foundations upon which many other elements of personalised medicine can be built, including infrastructure and improving genomic knowledge, that may serve to galvanise wider developments for personalised care.

Whilst genomics is a key element of personalised medicine, it is not the only element. In total 25 different technology areas (including genomic based technologies) that will potentially have a significant impact either on patient outcomes or on health system implementation were reviewed.

These technologies can broadly be grouped into one of the following four categories:

- Technologies for greater molecular characterisation of individuals or disease
  e.g. genomics, metabolomics, proteomics
- Technologies for personalised therapeutic interventions
  e.g. stem cell therapy, genome editing/therapy, robotics
- Technologies for personalised disease and health monitoring
  e.g. consumer mHealth apps, digitally enabled wearables and sensors
- Underpinning and enabling technologies to transform the performance or capabilities of other technologies
  e.g. artificial intelligence and machine learning, microfluidics, nanomedicine

Seven areas were examined in greater depth due to (i) the near-term opportunities presented by the technologies to contribute to the greater personalisation of medicine, and/or (ii) their identification as key areas of strategic interest and importance to the health system. These areas were:

- Circulating tumour DNA (ctDNA) testing
- Pharmacogenomics
- Transcriptomics
- Pathogen genomics
- Regenerative medicine (specifically stem cell therapies and gene editing/gene therapies),
- Advanced image analysis for histopathology
- 3D printing

In analysing how the most promising applications of these technologies could be implemented the report sets out 53 key policy considerations for NHS England as it seeks to develop and deliver personalised medicine approaches that will contribute to the goals of the Five Year Forward View.

Realising the near term opportunities

Specific applications of each of the seven technology areas reviewed in greater depth offer near-term opportunities to realise the benefits of personalised medicine. Ensuring their potential can be fully realised into patient benefit is pivotal to raising awareness of the value of personalised medicine approaches in the short term and to accelerating the drive towards prevention and earlier disease detection in the medium to longer term.

The main themes emerging within each of the analysed areas are:

ctDNA testing

ctDNA testing is a form of genetic testing to analyse fragments of cell-free tumour DNA found in the bloodstream. The technology is having an impact on patients with non-small cell lung cancer (NSCLC) by increasing access to targeted therapies for those in whom solid tumour biopsy has failed. ctDNA testing can be used instead to inform treatment selection. It is likely that ctDNA testing could expand to other cancers within the next 1-3 years.

The health system will need to consider how to ensure that all eligible NSCLC patients can access the testing that is already available, and how current services can be supported and strengthened to deliver tests and expand as future uses of ctDNA testing become available.

Pharmacogenomics

Pharmacogenomics is the analysis of how genes affect an individual's response to drugs, with the aim of personalising therapy to maximise therapeutic benefit, and to avoid adverse drug reactions and undesirable side effects. Pharmacogenomic tests will be formally included among the genomic tests available as part of the National Genomic Medicine Service.

The appropriate uptake of pharmacogenomic testing can be supported through the incorporation of best evidence into UK guidelines, through training and development of the clinical workforce, appropriate clinical, laboratory and digital infrastructure, and through the collection of evidence of the impact of pharmacogenomic information on clinical decision making.

Transcriptomics

Transcriptomics is the study of RNA (ribonucleic acid) and how genes are expressed in a cell, tissue, or sample at a specific time point. There are a growing number of targeted gene expression tests emerging for early detection, prognosis, and therapy targeting – particularly for cancer.

The health system should prepare to respond to evidence around gene expression tests as and when it emerges, and consider how elements of existing laboratory genomics infrastructure could be used to support the timely implementation of transcriptomic testing when appropriate.

Pathogen genomics

Pathogen genomics examines the genome sequences of pathogens to enable more targeted management and control of infectious diseases. The utility of pathogen genomics in resolving challenging outbreaks within the health system has been demonstrated, and there is a firm evidence base for using whole genome sequencing for the management of tuberculosis.

The health system will need to determine how pathogen sequencing can be incorporated into infection control efforts when appropriate, especially for hospital based investigations or those falling outside the public health function remit of Public Health England (PHE), and how to access these services, for example by utilising existing sequencing provision.

Regenerative medicine

Regenerative medicine (stem cell therapies, gene editing and gene therapies) are treatments which seek to replace, repair or regenerate the body's cells, tissues and organs. A number of the regenerative medicine treatments offer potentially curative or long-term treatments for chronic diseases, and new opportunities for personalised cancer therapeutics using the patient's own immune cells.

Near-term and longitudinal planning – e.g. infrastructure development, workforce training, continued reassessment of regulatory structures and adapted methods for reimbursement – are all key to ensuring health system readiness for implementing these therapies as their number and range expand in the coming years.

Advanced image analysis

Currently most histopathology – the examination of tissue sections or blood samples on a glass slide – is carried out manually by scientists and doctors analysing slides under a microscope. Digital pathology processes capture slide images in a digital format so they can be stored, viewed, and analysed using a computer. This could facilitate advanced image analysis for histopathology

Histopathology has been highlighted as one of the areas that could be transformed by artificial intelligence (AI) technologies. However the digitisation of pathology workflows is the vital first step to harness the potential of computational approaches including artificial intelligence and machine learning for histopathology image analysis. Standardisation and multi-centre data collection will be crucial to advancing AI technologies for histopathology.

3D imaging and printing

3D imaging and printing is a manufacturing process used to create customisable objects by depositing or binding successive layers of material. 3D printed objects are facilitating the personalisation of medicine through the development of patient-specific anatomical models for surgical planning and the customisation of devices and implants for individual patients.

3D printing is a multi-use technology, but currently its implementation is fragmented and tends to be localised, and confined to specific clinical departments, or individual clinicians with knowledge of the technology. An NHS-wide strategy to support implementation of 3D printing is required to fully realise the benefits of this technology across the whole of the health system.

Strengthening the foundations for whole system transformation

In addition to technology specific policy considerations, there are cross-cutting aspects to the delivery of personalised medicine. These include top-down support for the implementation of new technologies such as:

- Harmonisation of methodologies and standards for data generation, capture, and analytics
- Engagement across the workforce around the benefits of personalised medicine approaches
- Mechanisms for sharing expertise
- Approaches for managing small groups of patients as personalisation results in more refined categorisation of disease

One of the most pressing cross-cutting requirements is the need for improved informatics infrastructure to collect, store, manage, share, integrate and analyse patient data. This is because many of the reviewed technologies can generate considerable volumes of data (e.g. genomics, metabolomics, wearables), or they may fundamentally rely on underpinning digital infrastructure to operate (e.g. genomics, medical imaging, artificial intelligence) as well as the digitisation of health records.

Whilst digitisation has been an ongoing aspiration of the health system, it has been challenging to implement. Without the underpinning informatics hardware and software solutions, progress towards greater personalisation will be stalled. However, if harnessed effectively, the data amassing from biomedical and digital technologies can provide better context to an individual's health. In turn, the effective flow of this patient information can enable greater coordination across the health system and greater personalisation of care. In a fast evolving digital-age it will be crucial that the health system's informatics solutions are sufficiently agile and flexible to respond to the evolving capabilities of biomedical and digital health technologies.

Conclusions

Personalised medicine holds enormous potential to transform healthcare in England and improve patient outcomes. Key to maintaining momentum towards greater personalisation in the long term are the near term opportunities set out in this report. The benefits for patients and the health system, including more precise diagnosis and prognosis, more targeted and personalised interventions, better understanding and prediction of individual disease risk, could together support more efficient and effective use of health system resources. These elements will be essential for delivering on the ambitions of the Five Year Forward View.

Each technology presents its own specific challenges, but with the increasing convergence of these technologies, successful utilisation will depend on a synergistic and coordinated approach to implementation. As the single biggest integrated healthcare system in the world the NHS is uniquely poised to achieve this.

Introduction

The National Health Service aspires to be recognised as world-leading in its development of personalised medicine approaches. Most importantly, it aims to be a health system delivering world leading outcomes for patients by leveraging the unique advantages of its integrated system to apply those approaches systematically and equitably on a population scale.

This report presents an evidence synthesis to inform the NHS as it seeks to develop its approach and policies to support the delivery of personalised medicine and realise its benefits for patients within the timescales of the FYFV.

In this chapter we set out the context, objectives, rationale and methodology for the review.

1.1 Background

In September 2016 NHS England set out its vision for personalised medicine and how it intends to build on the work undertaken as part of the 100,000 Genomes Project. In parallel NHS England is transforming genomic laboratory services with a view to moving towards a more nationally co-ordinated and efficient approach to service provision. These developments are taking place in the context of major efforts across the NHS to deliver on the goals and ambitions of the Five Year Forward View (FYFV). This strategy, which sets stretching targets for improving outcomes against a background of increasing activity and a financially constrained position, provides the envelope within which personalised medicine will be introduced.

More widely across government, the publication of the Accelerated Access Review and the industrial strategy policy (particularly for the life sciences sector) are re-emphasising the need for improvement in the effectiveness with which the NHS fosters innovation, in order to improve outcomes for patients, to support the national economic interest and ultimately to ensure the long term sustainability of the NHS.

With these foundational documents and strategies in mind, NHS England is seeking to understand in more detail - and to articulate - the near term opportunities and challenges to realising the benefits for patients of the delivery of personalised medicine. It seeks to do this by maximising the beneficial impact for patients of the transformational programmes underway in the field of genomics but also to integrate genomics, where appropriate, with a range of other biomedical and digital technologies to deliver more personalised healthcare across the widest possible range of clinical areas.

Achieving the goal of making personalised medicine a part of business as usual for the health system in England, as opposed to the frequently perceived position as a peripheral and potentially disruptive adjunct to mainstream care, requires a clear articulation to stakeholders within the system of what it can deliver for patients now and what policies need to be in place to realise these benefits.

PHG Foundation undertook a review of the personalised medicine technology landscape on behalf of NHS England and have analysed how some of these approaches - namely those ready for implementation now or within the timeframes of the FYFV - could be integrated most effectively within the context of the evolving genomics and wider services within the NHS.

1.2 Objectives

The aim of this report is to present an evidence synthesis to inform NHS England as it seeks to develop its approach and policies to support the delivery of personalised medicine and realise its benefits for patients within the timescales of the FYFV.

Specific objectives of the review are to:

- Inform NHS England of the developments in biomedical and digital technologies that have a sufficiently well-developed evidence base for validity and utility that they would be able to underpin the delivery of personalised medicine in the next three years
- Identify and describe specific examples of personalised medicine approaches that are either demonstrably ready for implementation now, or could be within the next three years
- Analyse how the identified new personalised medicine approaches could be implemented within the context of currently evolving genomics and wider biomedical services in the NHS and any adaptations or additions that would be necessary to integrate these new technologies
- To highlight key considerations for actions that NHS England could take to develop and deliver personalised medicine approaches that will contribute to the goals of the FYFV

1.3 Scope and definitions

NHS England has referred to personalised medicine as:

'a move away from a one size fits all approach to the treatment and care of patients with a particular condition, to one which uses new approaches to better manage patients' health and target therapies to achieve the best outcomes in the management of a patient's disease or predisposition to disease.'

For the purposes of this review we sought to develop a framework that distinguishes the technologies ascribed to personalised medicine from the many other technological and practice-based improvements in medicine that could also be argued to contribute to personalisation.

This framework, which incorporates the statements of rationale, places personalised medicine in the context of the development of improved clinical practice more widely and provides a clear case for the criteria applied in this report when including or excluding particular technologies and their applications for greater in-depth analysis for this review.

Statements of rationale

- Personalisation of medicine is a continuous, fundamental process that aims to improve the effectiveness and efficiency of clinical practice by better understanding how the unique biological characteristics of individuals and their social/environmental contexts contribute to their health and disease
- The growing personalisation of medicine is facilitated by the development of technology, knowledge and scientific understanding
- All medicine is personalised, but the extent of this personalisation varies
- Personalised medicine as a term has emerged as a way to encapsulate the use in clinical care of a group of technologies that are expected to have a particularly transformative impact on the ongoing process of personalisation in medicine
- The technologies synonymous with personalised medicine – such as genomics – are considered to warrant special consideration by health system leaders compared to other technologies that are also contributing incrementally to the gradual personalisation of medicine this is due to the scale of impact they are anticipated to have on patient outcomes and because of the scale and complexity of the challenges their implementation poses to health systems

Together with these statements of rationale the scope of this report is circumscribed by the following factors:

Time horizons

In line with the aim to inform and advise how NHS England could proceed to develop and implement personalised medicine interventions that would realise benefits for patients within the time scale of the FYFV, the technologies and their applications subject to greater analysis in this report (Chapter 5) will focus on implementation ready approaches or those that could feasibly be brought into service within the next three years (from 2017) i.e. up to and including 2020, as well as particular personalised medicine applications highlighted for consideration by NHS England. Whilst not the core focus of this report, the longer term opportunities and challenges relating to other technologies that fall outside this time frame are described.

Sources for research and case studies

In seeking to identify technologies and personalised medicine approaches to be considered, a global evidence base was consulted. Where possible, England or UK based exemplars of services that are at or near to implementation readiness were sought. Where these were absent in England but present elsewhere international examples of best practice were used.

Exclusions

The scope of this review excludes specific investigation into innovative medicines but takes account of technologies that enable the more appropriate and effective use of medicines.

Finally as the purpose of this review is to focus on the personalised medicine technology landscape, it does not cover in detail the important social, ethical, legal/regulatory and economical aspects relevant to the delivery of personalised medicine, although these topics are raised in the context of specific technologies.

1.4 Structure of the report

Chapter 2

Summarises the national level developments in core NHS genomics infrastructure as essential background to understanding the foundations being established for personalised medicine. This development will in many cases intersect with or underpin the delivery of other technologies within the personalised medicine scope.

Chapter 3

Looks beyond the applications contained within the genomics service provision and describes the range of other biomedical technologies purported to contribute towards personalised medicine, their potential or real world applications, and an analysis of whether the technology and its application(s) will contribute to the personalisation of medicine in the next three years.

Chapter 4

Describes the importance of digital infrastructure to delivering biological personalisation and the significant contribution of digital tools, devices and apps to diagnostic and therapeutic personalisation. This covers the individual groups of digitally driven or digitally enabled technologies, and the broader impact of the information revolution on personalised medicine.

Chapter 5

Reviews in greater detail the applications of specific biomedical or digital technologies identified earlier in this report as having the potential to contribute towards the personalisation of medicine in the next three years and analyse how these could be integrated into the health service and delivered in a way that realises benefits for the whole patient population.

Chapter 6

In recognition of the need to set short term goals in the context of longer term aspirations for transformational change, the last chapter summarises a longer term, more visionary perspective on how developments in technologies and knowledge could enable a 'whole system' transformation towards personalised medicine as the norm, and the impacts of such a transformation both for patients and UK PLC.

1.5 Methodology

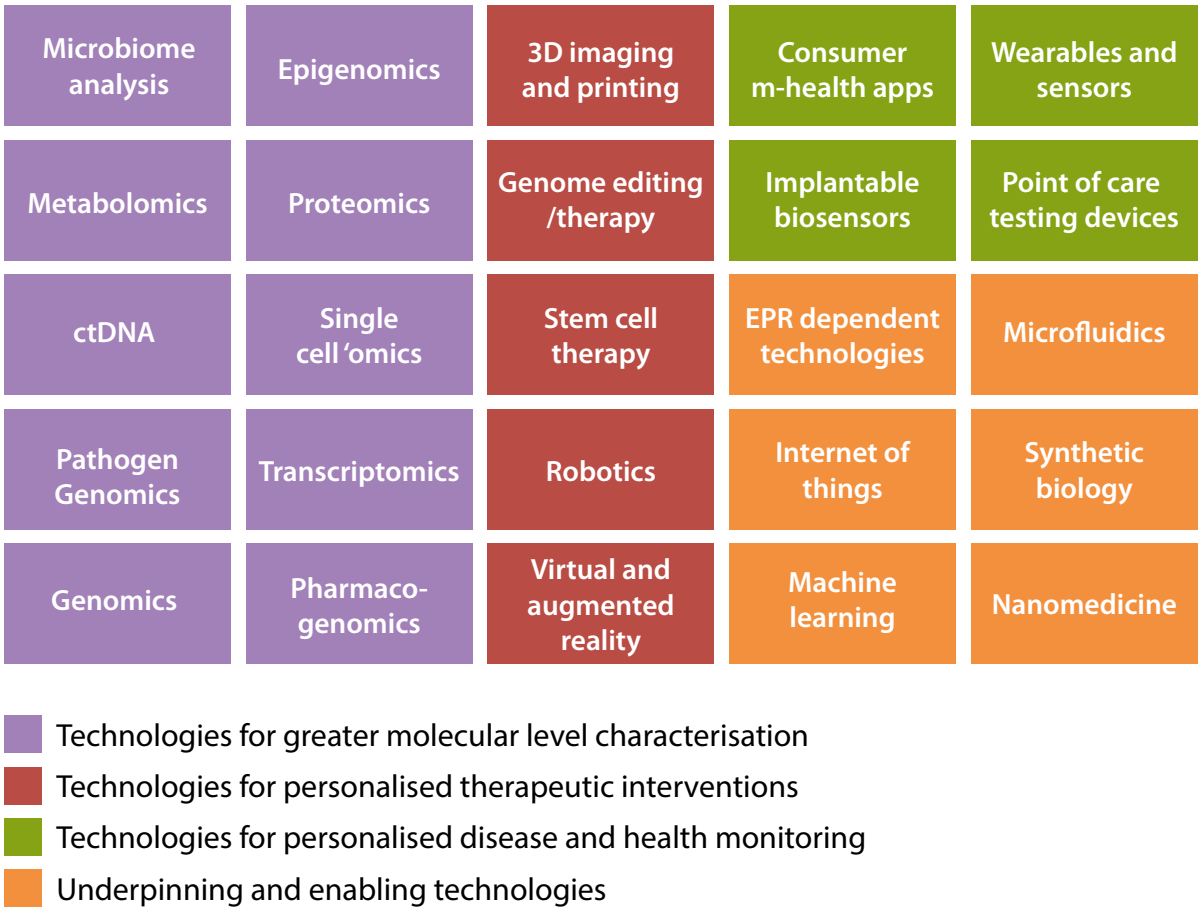
Technology identification and appraisal

Our assessment focused on technologies underpinning the delivery of personalised medicine from a publicly funded health service perspective. The long-list of technologies reviewed within this report is shown in Figure 1.1.

The identification and appraisal of novel technologies or novel applications of existing technologies for the personalisation of medicine was informed by desk-based research and analysis using a combination of public sources of information (e.g. NHS England strategy documents, National Institute for Health and Care Excellence (NICE), National Institute for Health Research Health Technology Assessments), grey literature, and international peer-reviewed literature. These sources were used to establish which of the identified technologies/applications had evidence of clinical validity and either existing evidence of utility, or a clear path to the acquisition of this evidence within the time horizon of the report (one to three years from 2017).

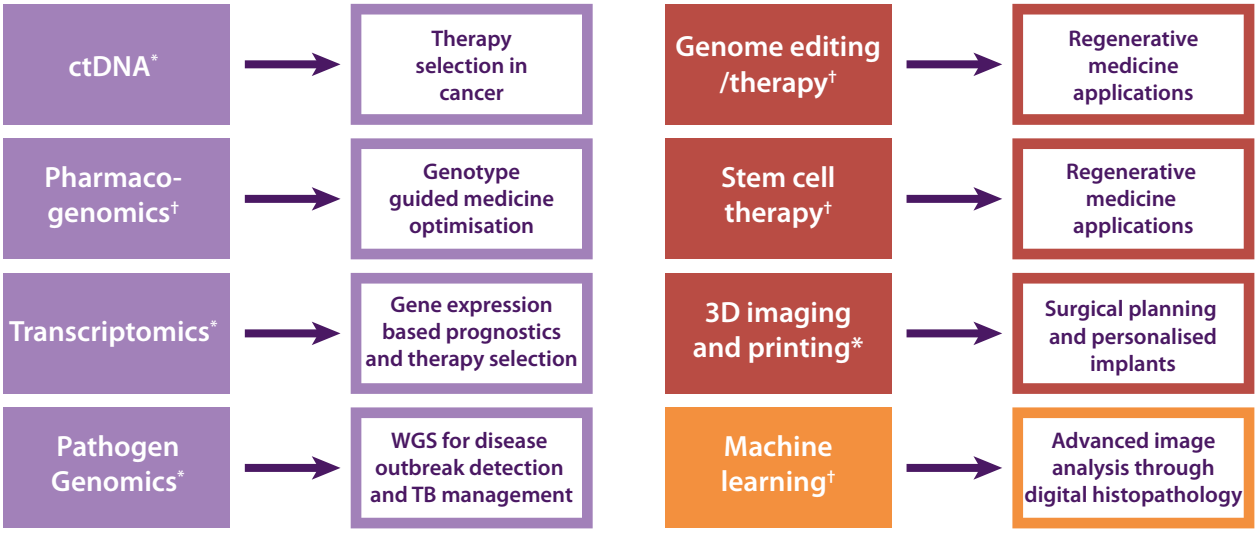
Our process for shortlisting technologies and their specific applications also considered whether or not the technology was already in routine use within the NHS, evidence of successful early adoption of the application within the NHS or other health systems, and whether there were significant challenges (e.g. logistical, evidential, educational, clinical, and financial) to its implementation in the NHS that require a system-led approach to overcome.

Figure 1.1: The long list of technology areas reviewed within this report.



This process generated a list of technologies and potential applications for further more detailed analysis (Figure 1.2).

Figure 1.2: Shortlisted technology areas reviewed in greater depth within this report.



* Technologies and their applications shortlisted for greater analysis based on the methodology and criteria described in this chapter.

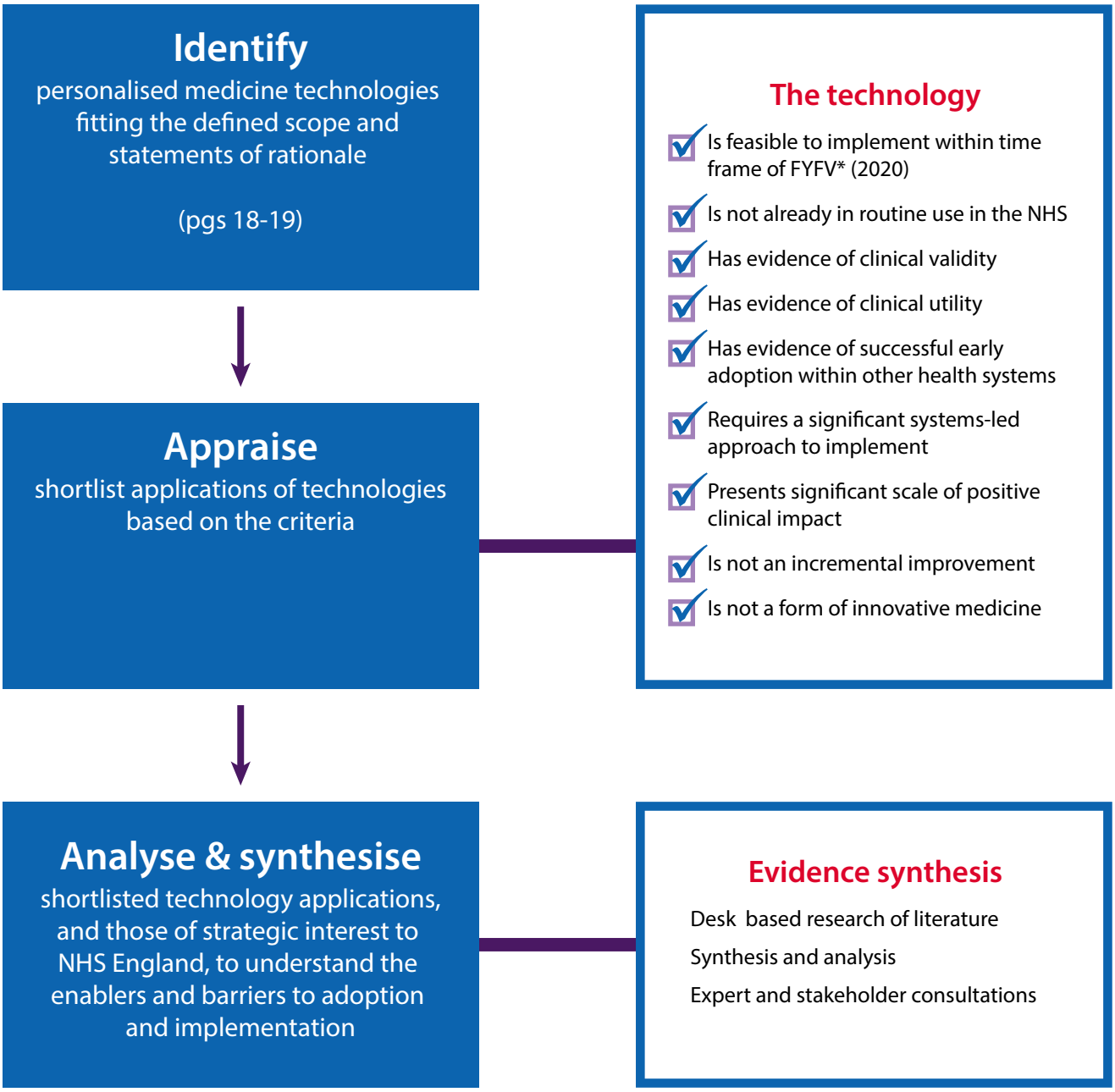
† Technologies and their applications highlighted as areas of key strategic interest to NHS England and therefore shortlisted for greater analysis.

Analysis of specific personalised medicine applications

The next phase entailed more detailed desk based research and interviews with experts and relevant stakeholders (Appendix 2) to understand the enablers and barriers to implementation and adoption of the applications identified, within the English NHS. The information gathered from desk and interview research was then synthesised to identify priority areas for the effective system-level implementation and adoption of the shortlisted technology applications.

The evidence synthesis undertaken for this report (including technology identification, appraisal, and in-depth analysis) was conducted between April 2017 - January 2018. The report was drafted in March 2018. The evidence base for many of the technologies areas continues to evolve since this evidence synthesis was performed.

Figure 1.3: Summary of scope and methods



* Five Year Forward View

The genomic revolution

Genomic information is an important component in the diagnosis, treatment and prevention of disease and a key element in personalised medicine. Genomic medicine is already an integral part of service provision within the NHS through current clinical genetics services - and is rapidly expanding to impact on other branches of clinical practice.

In this chapter we set out the key applications of genomics, the technological developments underpinning the expansion of clinical genomics, the changes afoot in England to create a National Genomic Medicine Service and supporting infrastructure, and how these changes will serve to galvanise wider developments in personalised medicine. We also identify a series of policy considerations.

2.1 Genomics – a key element in personalised medicine

The genome can be viewed as a blueprint for the construction, development and maintenance of an organism. The human genome varies between individuals and while much of this variation has no impact on our health, an important subset of variation contributes to our risk of disease. The magnitude of this contribution to disease risk varies widely. For the more than 7000 known rare diseases which collectively affect 1/17 of the population [1], a single genetic variant (or small number of variants) is the dominant causal factor in the development of the disorder.

In the case of cancer, multiple genetic variants may combine to contribute significantly to disease risk, but most combine with environmental factors such as smoking and obesity to drive the development of the disease. Even common diseases, such as type 2 diabetes, where the dominant contribution to their development appears to be our environment and behaviour, genetic variants play a small but potentially significant role in modifying our risk of developing the condition [2].

Due to its impact on health, analysis of genomic information forms an important component in the diagnosis, treatment and prevention of disease. Genomic medicine is already an integral part of service provision within the NHS through current clinical genetics services. However, the role of genomics within healthcare is rapidly expanding and it is increasingly impacting other branches of clinical practice. Furthermore, the ability of genomic information to act as a 'person/population specific biomarker' makes it a key component contributing to the foundations of personalised medicine [3].

2.2 Applications for clinical genome analysis

Clinical genome analysis is used in a number of ways by clinicians to manage health and disease. Most often this is in the context of diseases with a strong heritable component and is therefore undertaken within the context of clinical genetics. Broadly these can be classified as follows:

Diagnosis/classification of existing disease

Genetic testing of germline DNA can be used to provide a definitive diagnosis for those whose symptoms are suspected to have their origin in a rare genetic abnormality. It can also be used to distinguish between subtypes of rare genetic disease, or to distinguish cases of apparently common diseases (such as chronic kidney disease) that have genetic origins (and so are potentially heritable by other family members) from those that do not.

Information from genetic testing often has utility to the patient in knowing the cause of their condition and assisting reproductive decision making. It can also benefit family members, as it allows them to be tested and to understand their risk and take actions to reduce it. It may also enable more accurate prognosis, direct more effective therapeutic interventions or unlock access to disease-specific social and peer-to-peer support services.

Testing for disease risk

Analysis of germline genomic variation can be used to identify individuals who may be at increased risk of disease. Examples include:

- Antenatal testing for aneuploidies such as Down's syndrome, where genetic testing can be used to accurately determine whether or not a foetus is at risk of being affected with the disorder.
- Adult inherited cancer mutation testing, where healthy individuals with a strong family history of particular types of cancer can be tested for the presence of genetic variation that indicates they may be at much higher risk of developing these diseases in the future than the general population. This type of testing is not able to predict definitively that the patient will develop the disease, but can be used to guide decisions to take (or not take) risk reducing measures such as enhanced screening, chemoprophylaxis, or preventive surgery.
- Cascade testing such as for familial hypercholesterolemia, where relatives of a patient who has been diagnosed with the condition and has a positive genetic test, can also be tested to determine whether they are affected by the same disorder.

Medicines optimisation

Genetic testing is having increasing utility in guiding treatment decisions to select the most appropriate therapy for patients. The majority of NHS testing for this purpose takes place outside the context of the clinical genetics service. Testing can involve:

- Analysis of human germline DNA to test patients for rare genetic variant(s) that result in adverse drug reactions, or differences in drug metabolism. For example prescription of the anti-HIV drug Abacavir is done following genetic testing of patients.
- Analysis of human somatic tumour DNA is undertaken to identify if patients have a tumour type that is amenable to treatment with a particular drug. The use of a number of cancer drugs are now associated with companion diagnostics which involve analysis of tumour DNA [4].
- Analysis of pathogen genomes can also aid in treatment selection. For example, analysis of the *Mycobacterium tuberculosis* genome for drug resistance genes can help in treatment decisions (Section 5.3).

2.3 Evolution of genome analysis technologies

Techniques for genome analysis have been available since the 1970s and methodological developments have led to the availability of a number of different techniques for clinical genome analysis (e.g. polymerase chain reaction, next generation sequencing, array-comparative genomic hybridisation) (Figure 2).

Developments in next generation sequencing, which is multiplex in nature, has had the greatest impact on this landscape, by enabling an increase in testing capacity as well as throughput. It can be used to develop tests for conditions for which tests were not previously available and be used to analyse a larger number of samples.

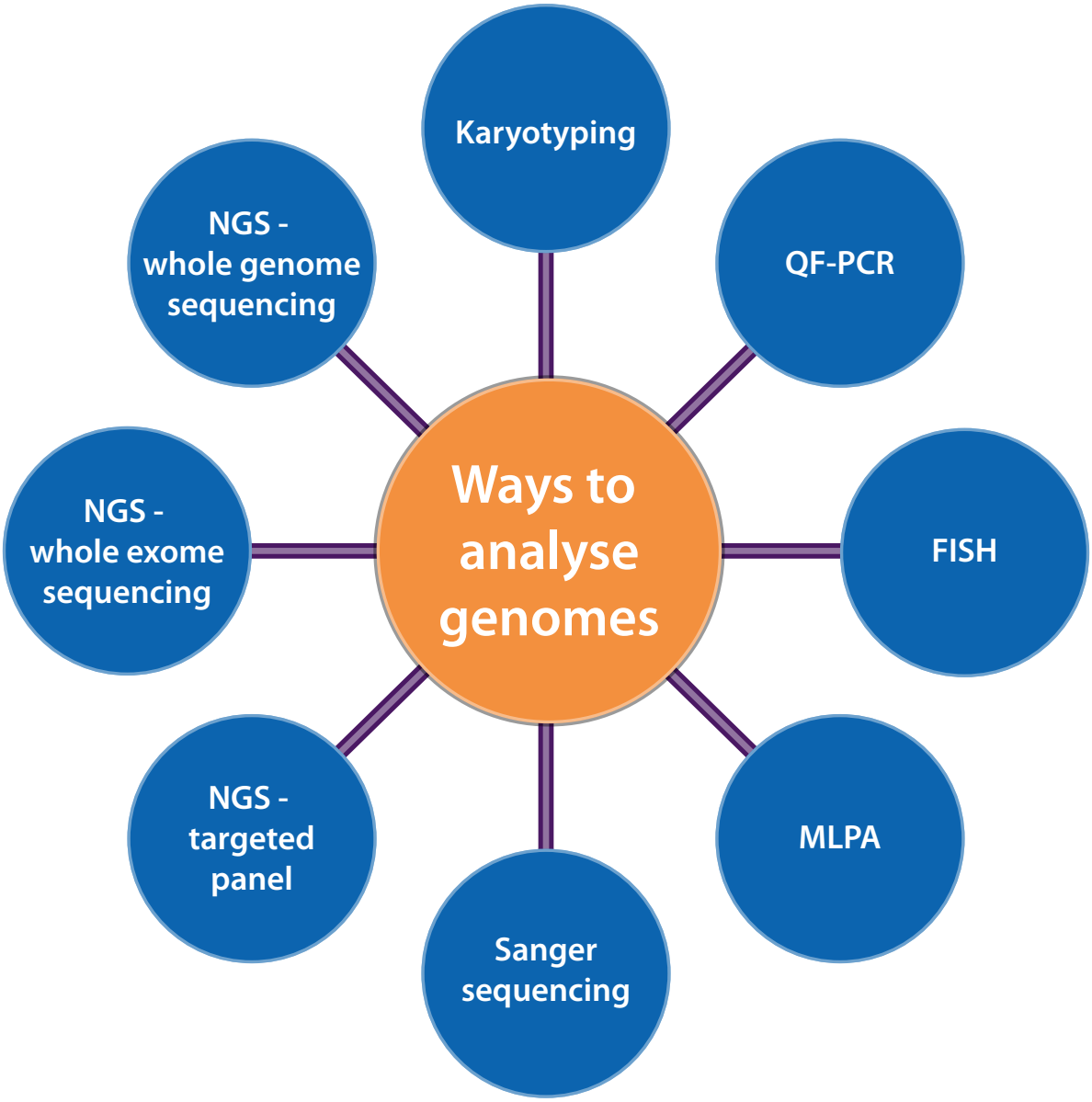
Technical capacity is also rapidly expanding in relation to the types and sources of DNA (e.g. cell free, tumour, single cell) that can be reliably isolated, sequenced and analysed. These two aspects are leading to a broadening scope of applications. Furthermore, these technologies are not restricted to analysis of human germline DNA, but also underpin the development of many other 'omics applications (e.g. transcriptomics, microbiome analysis, ctDNA, pathogen genomics etc.). Consequently, an effective genomic service will be able to integrate a wider spectrum of applications.

Currently, multiple different techniques for genome analysis are utilised in clinical practice. This is because no one technology is able to effectively detect the full spectrum of genetic variations (ranging from deletions of parts of chromosomes to point mutations affecting single base pairs) that underlie different diseases.

The use of next generation sequencing and the implementation of whole genome sequencing (WGS) may alter this in the future as the evidence base grows and the potential for a single technique that can be applied to detect the whole spectrum of genetic variation is better understood. In principle it could be applied to test for multiple disorders and in a number of different contexts as is currently being demonstrated through the 100,000 Genomes Project for rare diseases and cancer. However, current limitations in sequencing technologies mean that WGS cannot as yet replace all techniques.

Technical developments in single molecule long read sequencing may overcome some of the shortfalls of current platforms [5]. The implementation of newer sequencing technologies will be influenced by their accuracy, throughput and cost.

Figure 2: Different assays used in clinical genome analysis. Choice of assay is dependent on consideration of both technical and practical criteria.



Technical criteria

- Clinical question
- Genes/genomic regions to be analysed
- Type of genome variation

Practical criteria

- Speed
- Cost
- Need

2.4 Current clinical genetic testing services in England

NHS clinical genetic services include a range of clinical and laboratory services, delivered from a network of 23 Regional Genetics Services (RGS) across the UK, 17 of which are based in England. The RGS provide an effective, coordinated service to patients and families with inherited diseases, with most molecular, genetic and cytogenetic testing taking place in genetic laboratories associated with RGS. They also provide a source of genetic tests and specialist interpretation for clinicians in specialities outside of clinical genetics. Some centres use commercial testing facilities to provide specific tests or to assist with fluctuations in workload.

Not all testing associated with inherited diseases takes place in the context of a regional genetic laboratory. Specialist biochemistry laboratories, newborn screening laboratories and haematology laboratories also provide essential testing services, however, with the exception of the latter these tests are not DNA-based. Conversely, not all clinical genome analysis occurs in the context of clinical genetic laboratories, with some analysis occurring in other pathology laboratories. The repertoire of genomic analysis provided by laboratories varies regionally in England based on funding decisions made by commissioners of individual services.

The existing model of laboratory provision is currently in under review, with NHS England tendering for the provision of a National Genomic Testing Service which will consolidate and reconfigure existing clinical genetic laboratory services into a maximum of seven Genomic Laboratory Hubs.

2.5 Creating a National Genomic Medicine Service

The evolution of genomics in healthcare is being driven by the convergence of a number of factors that are catalysing changes to the existing model of genomic service delivery. These include:

- Rapid advancements in sequencing technology and informatics
- Establishment of the 100,000 Genomes Project [6] and WGS testing in the NHS
- Large-scale sequencing of those participating in the UK Biobank
- Increasing mainstream applications of genetics – i.e. across different areas of clinical practice

This, together with the recognition that effective genomics services will form the foundations upon which many of the other elements of personalised medicine can be built, led the NHS England Board to agree a strategic approach for building a genomic medicine service from 2018/19 [3,7]. The aims of the service are to:

- Ensure comprehensive and equitable access for the entire population
- To provide prompt diagnosis and personalised care
- Form appropriate collaborations with academia, UK life sciences sector to support learning, research and development
- Retain and build the political, ethical and moral trust of the UK in genomic medicine

Key components of the National Genomic Medicine Service

The National Genomics Medicine Service will operate to common standards and protocols to provide population-based care, supported by a national laboratory network and a National Genomic Test Directory that will cover the use of all technologies from single gene to whole genome sequencing in the NHS in England. These will be underpinned by informatics architecture, data storage and sharing mechanisms, clinical interpretation pipelines and whole genome sequencing from a single provider. Included in this strategy is the development of partnerships with academia and the life sciences sector to harness and support development of an UK genomic knowledge base.

Oversight and coordination of activity across these components will be carried out by a NHS England Genomics unit.

The service will bring together restructured clinical genetics services, evolved NHS Genomic Medicine Centres and the new hubs as an integrated service delivery model. The current role of NHS GMCs is to support delivery of the 100,000 Genomes Project and establish infrastructure to make genomic medicine a routine part of NHS care.

As the field evolves, NHS GMCs are expected to play a role in consolidating learning from the 100,000 Genomes Project, supporting the establishment of genomic multi-disciplinary teams and driving medicines optimisation, appropriate prescribing and personalisation of interventions.

National genomic testing service

As part of this reconfiguration, NHS England is tendering for the provision of a National Genomic Testing Service in England. The aim of the procurement is to consolidate and reconfigure existing genetic laboratory services and to create up to seven Genomic Laboratory Hubs (GLHs) to provide a world class resource in the use of genomic technologies for rare and acquired disease and cancer. The new service is expected to be operational from 1st October 2018.

It is envisioned that GLHs will consolidate the existing regional genetic laboratories, thereby acting as a single point of delivery of the majority of the genomic tests for their geography. They may subcontract for a specific repertoire of specialist genomic tests they cannot provide directly. Consequently, they will work as part of a GLH National Network and a Genomic Local Laboratory Network to deliver a National Genomic Testing Service, including provision of genomic tests as set out in a National Genomic Test Directory.

Along with operating within a national testing network, these hubs will be involved in planning and developing the workforce and in the promotion of research and innovation.

The National Genomic Test Directory

For the first time a national testing strategy in the form of a National Genomic Test Directory will list all the genomic tests that will be available on the NHS in England. This will be updated annually in line with emerging evidence.

There will also be a process that will allow tests to be added to the Directory before the annual refresh. Tests based on analysis of DNA, initially for inherited disorders, germline and somatic tests for cancer and those that enable targeting of treatments will be included in the Directory.

At this stage tests based on analysis of pathogen DNA and those that are not DNA-based (e.g. newborn screening, biochemical antenatal screening) are not included within the scope of the Directory, neither are tissue typing and tests for preimplantation genetic diagnosis.

The tests are broadly categorised under three groups:

- Core tests to be delivered by all GLHs
- Specialist tests including non-invasive prenatal testing to be provided by appointed National Specialist Test Providers
- Whole genome sequencing tests

GLHs will access WGS testing from a national WGS provider secured by Genomics England. The GLHs are expected to work collaboratively with Genomics England, the WGS provider(s) and a National Bioinformatics Service in delivering these.

2.6 Moving forward: policy considerations

As our knowledge of the genetic basis of disease increases and new clinical interventions are developed for a specific genetic status, the usefulness and impact of clinical genome analysis will expand. Laboratory capacity for genomic analysis therefore is expected to increase in order to provide the population health benefits of these developments.

Current platforms offer the opportunity to simultaneously consolidate, simplify and also broaden the coverage of the existing complement of tests due to their multiplex nature.

Implementation of these technologies differs from previous innovations, whose development was incremental and additive in nature. Consequently, their effective implementation over the next five years depends largely on the progress made in developing the infrastructure, informatics and scientific and clinical expertise needed to deliver a radical shift from an incremental and additive technology to one that is multiplex and multi-use in nature.

Efforts are already underway to create this infrastructure and key elements, including the informatics infrastructure and a genomics knowledge base. This, together with efforts to link routine care with research activities, will enable support for ongoing learning and promoting novel pathways of care.

Much of the technological considerations relevant to genomic technologies also have implications for other 'omics platforms and their impact on personalised medicine. As such, the foundations being established for the NHS Genomic Service will be an important stepping stone to integration of a broader range of 'omics technologies into healthcare.

Summary

Genomics is a key element of personalised medicine and the UK has a long history of developing the clinical applications from genomic research to improve the care and treatment of patients. With the significant transformation of NHS genetic testing services in England, it will be possible to accelerate the implementation of new testing for greater patient benefit.

The emerging technology landscape

This chapter sets out the landscape of technologies that have been proposed to contribute to personalised medicine. In technology-by-technology reviews we describe the current state of activity and healthcare applications, promising areas of research and development and an assessment of whether any specific applications of the technology may impact the personalisation of medicine within the next one to three years (as per the methodology in Section 1.5), if so, these are reviewed in greater depth (Chapter 5).

For technologies and their applications further from impacting personalised healthcare, we reflect on the factors that may influence their development to the point of clinical readiness. These may include step-changes in underpinning technologies or knowledge upon which clinical developments depend, or strategies that could potentially accelerate the clinical utilisation of the technology.

3.1 Technologies for molecular level characterisation and stratification of individuals

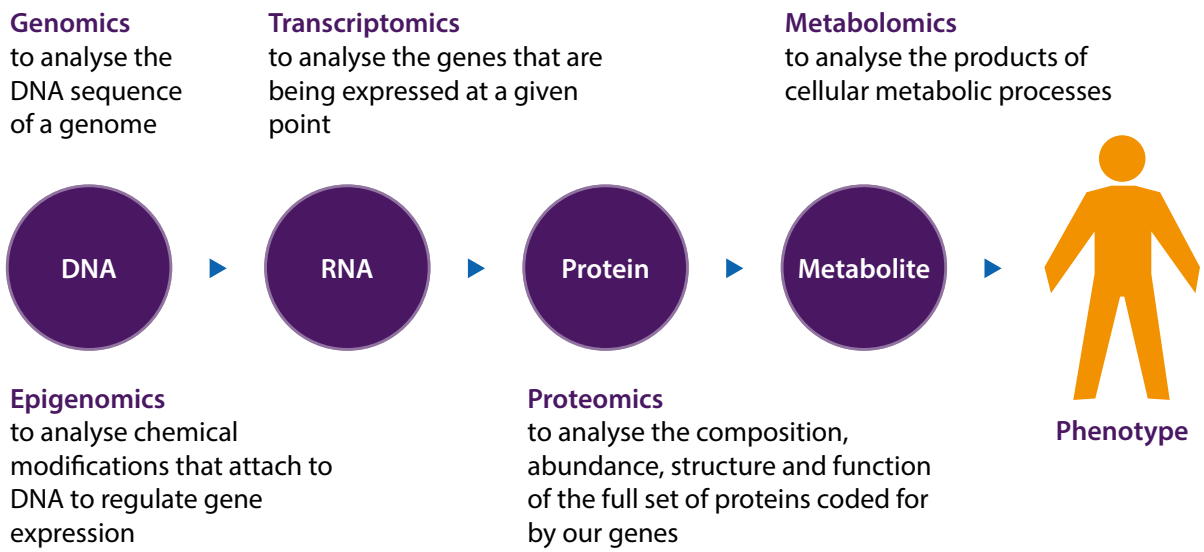
The preceding chapter described the applications of genomics and national level developments in core genomics infrastructure. Whilst these changes will enhance the application of genomics, information from the entire functional genomics pathway (i.e. how genomic information is expressed in our cells) is also vital to improving our understanding of:

- The biological significance of genomic variation
- Gene-environment interplay in health and disease
- Dynamic changes in cellular molecules during disease progression

Hence, we begin by reviewing the 'omic technologies and 'omics-based approaches that have been purported to contribute towards the personalisation of medicine.

The term 'omics refers to a group of technologies that enable the global assessment of the various types of molecules (e.g. DNA, RNA, proteins, and metabolites) that make up cells (Figure 3).

Figure 3: 'Omics technologies for the global assessment of different molecular constituents of cells



The typically high throughput nature of 'omics approaches is allowing more detailed molecular characterisation of individuals. This information can be leveraged to refine the stratification of individuals or their disease into subgroups based on differences in susceptibility to or severity of a specific disease, or response to a specific treatment. Ultimately 'omics analyses can inform more precise diagnosis or prognosis, and more targeted treatments and interventions.

Proteomics

The proteome consists of all of the proteins present in a cell at a particular time. Proteomic analysis measures these proteins, for example to understand differences between healthy and diseased cells and whether changes are caused by or are causing disease. Proteomics can provide information about the dynamic changes in molecular phenotype and show how widely genes can be expressed in different contexts. In recent years the field has advanced as a result of research leading to the growth of DNA and protein sequence databases, and in particular due to improvements in mass spectrometry technology which is the principal technology used to analyse the proteome.

What is the status of proteomics health applications?

Some of the most long-standing clinical tests available rely on the measurement of individual proteins, for example liver function tests measure levels of liver enzymes in the blood and blood albumin (made by the liver) as an indication of overall liver health. Implementing new tests that measure individual biomarkers does not usually pose a significant systems implementation challenge if there is demonstrated clinical utility.

The challenge has been to bring protein analysis to the next level, understanding how groups of proteins or even whole proteome analysis – where all of the proteins in a cell at a given time are analysed – can be used to develop targeted interventions.

Currently the most tangible applications of proteomics is the analysis of specific target proteins rather than whole proteome analysis.

Targeted protein analysis for informing cancer treatment and risk

There are a limited number of panel based (more than one protein on the same test) or targeted protein-based tests in development. PD-L1 protein testing is available for informing therapy selection in non-small cell lung cancer; to prescribe nivolumab, a monoclonal antibody [8]. Implementation of this test did not present a significant system challenge.

The Overa test, which combines five immunoassays into a single test, aims to help decision-making as to whether women presenting with a pelvic mass have a high or low risk of ovarian cancer. The test is US Food and Drug Administration (FDA) approved and CE marked (European Economic Area certification), however recently updated guidelines from NICE do not recommend routine adoption, stating that more research is needed into its effectiveness in different sub-groups of women [9].

Clinical proteome analysis

Wide-ranging or whole proteome analysis is still very much in the research phase and is focused on understanding the difference between normal and diseased states and the identification of biomarkers for diagnostics and stratification.

The clinical translation of proteomics is currently restricted by the technical challenges and complexity of analysing the proteome:

- There are more than 10 times as many proteins in the human body as there are genes (250,000 proteins coded by 21,000 genes)
- The proteome is dynamic – protein levels fluctuate with time, in different physiological situations and vary by cell/tissue type
- The dynamic range – levels of different proteins vary by many orders of magnitude e.g. the blood protein albumin is around a billion times more concentrated than the immune system protein interleukin-6. Developing a single assay capable of measuring the full concentration range of multiple proteins is a technological challenge
- Due to the above factors, reproducibility of results is challenging

Technological advances in mass spectrometry, such as SWATH-MS, are enabling more accurate and higher-throughput generation of protein maps in samples and may help to accelerate the identification of novel protein biomarkers. Further research is needed to demonstrate how this type of technology could be used in the clinic and to identify and validate biomarkers.

The Medical Research Council-funded Clinical Proteomics Centre for Stratified Medicine is among those working in this area. Collaborations across the proteomics research community will be key to the development and adoption of data standards, quality control, and standard operating procedures.

Summary

Proteomics is essential to understanding the functional effects of coding genomic variants. 'Proteogenomics' – combining genomics and proteomics analysis – will further enhance understanding of the molecular mechanisms underpinning health and disease. Currently whole proteome analysis is predominantly a research tool, and further evidence is needed to recommend clinical adoption of targeted protein analysis, therefore this area was not taken forward for further analysis in this report.

Epigenomics

Epigenetics describes physical or chemical modifications to DNA that affect levels of gene transcription within cells. These modifications vary between cell-type and can occur in response to environmental cues. The epigenome describes the set of epigenetic changes that exist in a cell or tissue at a given time.

A growing body of evidence now suggests that epigenetic changes driven by gene-environment interactions may cause or modify disease by altering gene expression. Within medicine, epigenetic tests that measure the alterations to DNA in a restricted set of genes are being developed, in particular, changes that indicate whether or not a person might have a particular disease. These types of tests could contribute to personalised medicine by diagnosing patients more accurately, detecting disease earlier, or by informing treatment decisions.

What is the status of epigenomic health applications?

Early detection of cancer

Currently the most advanced clinical applications of epigenomics are in cancer, particularly around early detection/screening. A number of panel based or single site tests that have an epigenetic component have been developed for colorectal and lung cancer, which have FDA approval or a CE mark (Table 3.1). Some colorectal cancer tests aim to detect epigenetic changes in colon cells extracted from stool samples, and others using liquid biopsy to detect epigenetic changes in chromosome fragments circulating in the blood. Further tests in these and other cancers, and other diseases, are under development [10].

Table 3.1: FDA approved and CE marked tests with an epigenetic component

Test	Cancer type	Company	Approval
Cologuard	Colon	Exact Sciences	FDA
NuQ®X001S	Colon	VolitionRx	CE marked as IVD* (EU)
Epi proColon	Colon	Epigenomics AG	CE marked as IVD (EU), FDA
Epi proLung	Lung	Epigenomics AG	CE marked as IVD (EU)

**In vitro* diagnostic medical device

A challenge to the clinical uptake of these tests is the current paucity of evidence towards their clinical utility and cost effectiveness, and in some cases low test sensitivity. For example sensitivity of one test, Epi proColon, has been reported as being around only 50% [11]. Clinical trials are underway for these tests, including Epi proColon and Cologuard, to study the impact of its use in average risk patients [12]. The results from trials such as these are needed to determine the clinical effectiveness of this type of test, and further work is needed to determine their cost effectiveness. Currently these types of tests are not under consideration by NICE. It is unlikely that tests utilising epigenomics will present as a major service requirement within the next three years.

Genome-wide epigenomic analysis, and systematic epigenomic analysis for diagnostics, treatment targeting, or prognostics

In cancer, potential future applications of epigenomics may include genome-wide epigenomic analysis of tumours to identify novel cancer drug targets [13], using epigenetic markers to guide treatment [14] or determine disease prognosis [15]. Currently much of this work is within the research phase and there are no clinically validated methylation profiles for tumours being evaluated in clinical trials for guiding prognosis or therapy selection. Other disease areas with a epigenetics research focus include immunological disorders such as Lupus erythematosus, Alzheimer's disease and metabolic disorders [16].

Further research and clinical trials are needed to demonstrate the clinical validity and utility of epigenomic analysis and also how epigenomic data might be used alongside other disease relevant information such as genomic or biomarker data.

Summary

Epigenomic analysis is a well-established technology with a strong research base. Since most development around this technology remains within the research phase, and evidence is still being generated for the few clinical tests that are emerging, this technology was not shortlisted for greater analysis in this report.

Transcriptomics

Transcriptomics is the study of the transcriptome, the sum of RNA (ribonucleic acid) present in a cell, tissue, or sample at a specific time point – and as such is a measure of gene expression. There are many different types of RNA. The most broadly studied form is messenger RNA (mRNA) – the key intermediate between the genome and proteome – which specifies the amino acid sequence of resulting proteins.

The most widely used technologies for examining gene expression include RNA sequencing, microarray profiling, and qRT-PCR. Microarray and qRT-PCR panels can assess the expression of specified and known sets of genes. RNA-sequencing is a high-throughput approach to examine the whole transcriptome of a sample, including transcripts for which the sequence is unknown. Additionally, compared to microarrays, RNA sequencing offers a broader dynamic range and higher sensitivity to detect and quantify especially low or high abundance transcripts.

These technological advances are generating vast amounts of transcriptomic data for the analysis of differential gene expression signatures between disease and healthy states. This information may help identify disease-relevant biomarkers.

What is the status of transcriptomics-based health applications?

Gene expression panel tests for early detection, prognostics and therapy targeting

A number of gene expression profiling (GEP) tests have been developed and or are in development internationally. These range in application from GEP tests for cancer treatment stratification to early detection of obstructive coronary artery disease or diabetes, and most utilise microarray or qRT-PCR techniques [17-21].

Many tests are available for use in post-operative breast cancer and in some instances offer cost saving through avoidance of chemotherapy and may increase patient confidence in treatment decisions.

A number of tests are already in use in the UK and internationally, although uptake is restricted by gaps in evidence relating to patient benefit and survival outcomes. At the time of our analysis, one GEP test, Oncotype DX, had been recommended by NICE [22] as an adjunct diagnostic for the assessment of post-surgery breast cancer tumour recurrence risk and the associated likely benefit of chemotherapy treatment. However, new guidance is due and consultation is ongoing. Updated draft guidance regarding Oncotype DX and several other GEP tests for informing adjuvant chemotherapy choice is expected to be published by NICE in September 2018.

Whole transcriptome analysis

Transcriptomics is extensively used in research to measure changes in the gene expression profile of cells and tissues. Typically these analyses aim to investigate the underlying changes to molecular pathways associated with health/disease state; or to examine the functional consequences of genomic variants.

Direct clinical applications of whole transcriptome analyses are unlikely to manifest in the next one to three years because currently:

- Knowledge of disease-associated transcriptomic signatures is still limited
- The cost and analytical burden of analysing whole transcriptomes vs targeted transcripts is currently high
- Reproducibility of data can be challenging as RNA is an unstable molecule and is dynamic in nature i.e. as with proteins, mRNA levels can fluctuate across time

Improvements in sequencing technology, including 'direct' sequencing of RNA molecules as they exist *in situ* [23] as well as efforts to develop best practice and standardise experimental and analytical approaches [24] will facilitate future clinical adoption of transcriptomics.

Summary

An expanding body of transcriptomics research is helping to discern functionally relevant patterns of gene expression in health and disease; however, clinical translation of broad transcriptomic analysis is currently restricted by challenges in data analysis and clinical validation of observed disease-specific expression changes. By contrast, the number of targeted gene expression tests in development and in use is growing, therefore gene expression panel-based tests were shortlisted for further analysis.

Metabolomics

Metabolomics is the study of products of metabolism formed from intracellular biochemical reactions. Collectively, all metabolites of low molecular weight (50-1500 Daltons) within a biological system – from a cell, organ or whole organism – are referred to as its metabolome.

Metabolites are generated from the degradation of larger molecules synthesised internally, such as gene-encoded proteins, or obtained from external sources, such as dietary nutrients or drugs. The metabolome is therefore a highly personalised readout of metabolism and provides a retrospective and comprehensive overview of the metabolised products of gene expression and externally derived substances.

Metabolites can be detected in samples commonly collected in clinical practice including urine, blood, and tissue biopsies. The most commonly used laboratory techniques in metabolomics are mass spectrometry and nuclear magnetic resonance spectroscopy. Whilst mass spectrometry is enabling the detection of thousands of metabolites at very low concentrations within a single sample [25], no single analytical technique is currently capable of identifying and quantifying all metabolites simultaneously in a single sample.

An existing established clinical application of metabolic profiling in the NHS is the newborn blood spot screening programme for rare inherited metabolic diseases that affect key metabolic pathways [26]. Beyond newborn screening, clinical applications of metabolomics are predominantly in pre-clinical stages of development.

Metabolic data could reveal novel and more precise biomarkers of clinical relevance and improve our understanding of disease mechanisms.

What is the status of metabolomics health applications?

Early detection – pre-cancer

Early detection is one of the most promising future clinical applications of metabolomics. One example is a urine-based screening test for pre-cancerous colonic adenomatous polyps (PolypDx™). This test offers greater sensitivity for polyp detection than current colorectal cancer screening methods (which test for the presence of blood in faeces), and may enable earlier detection and removal of colonic polyps prior to their progression to colon cancer [27–29].

However, evidence of clinical benefit relating to prevention of colon cancer and improved patient outcomes is currently limited. PolypDx™ is commercially available in the US and has received patent approval in Europe, but has yet to obtain FDA approval and a CE mark for *in vitro* diagnostic use.

Systematic metabolome analysis

There is an active research base to identify clinical biomarkers in a range of disease states including cardiovascular disease, metabolic syndrome and cancer. Broad metabolic profiling, which is sometimes also combined with genomic analysis, has generated insights into the disease associations of certain metabolic traits, within the contexts of obesity [30–32], hypertension [31], kidney disease [33], insulin resistance [34], type 2 diabetes [35] and cancer [36].

Progress has also been made in identifying dietary metabolic biomarkers in urine, which may facilitate more accurate characterisation of dietary habits, disease risk stratification and monitoring of population health [37].

The value of metabolic analysis in predicting drug responses is also being investigated and may offer potential for 'pharmacometabolomics' to inform personalisation of drug therapy in the future [36– 39].

The broader clinical use of metabolomics is predominantly restricted by the complexity of analysing the metabolome and challenges in identifying metabolites which may serve as clinically useful biomarkers including:

- Challenges in reliably discriminating between metabolites
- Variation in experimental conditions and metabolite identities among research groups [25, 40]
- Lack of clinical validation of metabolites identified as biologically significant in research studies

Addressing these technical challenges and harmonising experimental techniques, analysis and reporting will be key to expediting the clinical application of metabolomics.

Summary

Whilst metabolomics research is generating many clinically relevant findings, a significant expansion in the number of clinically validated biomarkers is not expected within a one to three year time frame, so the technology was not shortlisted for greater analysis in this report. Nevertheless, metabolomics offers great potential for future applications of personalised medicine, and as clinically validated metabolites are identified their analysis could in principle be integrated with relative ease since mass spectrometry is an established technique in the NHS.

Pharmacogenomics

Pharmacogenomics (PGx) is the study of how genes affect an individual's response to drugs, with the aim of personalising therapy to maximise therapeutic benefit and to avoid adverse drug reactions (ADRs) and undesirable side effects.

Pharmacogene variants have been associated with differences in drug absorption, metabolism and activity, which may result in suboptimal dosing regimens and reduced effectiveness of treatment, or predispose individuals to toxicity and adverse effects. ADRs contribute to 6.5% of hospital admissions [41] and are estimated to cost the NHS one billion pounds annually [42].

PGx data can help to inform the most effective drug therapy plans for patients based on their individual genetic profiles and may enable migration from traditional trial-and-error prescribing that can lead to adverse clinical outcomes including morbidity and mortality resulting from ADRs, suboptimal clinical management due to drug intolerance, and avoidance of therapy by patients.

Work is underway on building the evidence base to enable the evalutation of PGx testing for inclusion in the National Genomic Test Directory from 2019/20. This application of genomics was identified by NHS England for further exploration as they seek to build PGx testing into the NHS Genomic Medicine Service.

What is the status of pharmacogenomics health applications?

Drug dosing guidelines providing recommendations for specific gene-drug pairs have been published by groups in the Netherlands and US [43–45]. Almost 15% of medicines evaluated by the European Medicines Agency (EMA) report pharmacogenetic associations in their product information [42, 46]. Guidelines are available for many commonly prescribed drugs, including those for pain relief, cardiovascular disease, anticoagulation, diabetes, mental health disorders and cancer.

Despite the accessibility of clinical guidance, no nationwide PGx testing programmes are currently in place in the UK or internationally, and access to PGx testing is limited to selected centres.

Precision drug dosing: genotype guided prescribing to improve drug efficacy and avoid adverse events

Genetic information can be used to identify the underlying mechanisms of disease and to refine clinical diagnoses, which enables the use of more targeted therapies to optimise treatment. One such example is the use of *PCSK9* inhibitors to treat cases of familial hypercholesterolaemia due to mutations in the *PCSK9* gene.

Many additional genetic associations with drug responses do not relate to the direct action of drugs at their target sites, but instead affect drug absorption and metabolism. Genotype guided dosing strategies of warfarin have been developed taking into account variations in just two genes, which leads to improved control of anticoagulation.

PGx also has the potential to replace some pre-screening tests of enzyme activity that may be performed prior to commencing treatment, such as the immunosuppressant drug azathioprine which can cause bone marrow suppression if insufficiently metabolised by the enzyme thiopurine s-methyltransferase (TPMT).

Where strongly indicated, single pharmacogene testing is available in the NHS. This includes pre-treatment screening for the *HLA-B*5701* allele prior to commencing abacavir medication in HIV patients.

Testing for very few additional pharmacogenes is potentially available as part of unrelated gene panels via the UK Genetic Testing Network, but referrals are highly unlikely to meet testing criteria unless also clinically indicated for diagnostic purposes.

In the future, PGx tests will be included on the genetic test directory for the new national genomics laboratory service (Chapter 2).

Informing cancer therapy: somatic and germline PGx

Identification of novel somatic genetic mutations occurring within cancer cells has led to the development of targeted therapies, which require companion diagnostic testing to determine whether treatment would be beneficial. *BRAF*^{V600} genetic mutations are present in approximately 50% of cases of metastatic malignant melanoma, and can be targeted using *BRAF* inhibitors to increase overall and progression-free survival.

Germline genetic variants can also affect the metabolism of drugs used in cancer therapy and predispose individuals to serious side effects, including bone marrow toxicity. Such genes include *DPYD*, which informs dosing of the chemotherapy drugs 5-fluorouracil and capecitabine, and *CYP2D6*, which has been associated with the effectiveness of tamoxifen therapy.

Progress in broadening the use and integrating PGx into health services has been hindered by several reasons. One is the limited set of evidence of clinically validated genes and variants, for which the outcomes of ongoing clinical trials will be key; including a major clinical trial to assess the value of **Pre**emptive **P**harmacogenomic testing for prevention of **A**dverse drug **Re**actions (PREPARE).

Even for those of genes with a strong evidence base implementation is lagging due to:

- Laboratory capacity to perform PGx testing
- Awareness among relevant healthcare professionals of PGx testing and its implications for patient care
- Lack of PGx clinical guidelines approved for use within UK health systems
- Uncertainty around the mechanisms for incorporating PGx data into clinical decision making and care pathways
- Lack of integration of PGx data including into electronic health records, electronic prescribing systems and clinical decision support tools [47]

Summary

Pharmacogenomic testing is a powerful example of personalised medicine to inform more tailored and optimal therapy and is arguably an application of genomics that has to date remained underserved. Its potential inclusion within the National Genomic Test directory presents a critical opportunity to optimise the integration and impact of PGx into healthcare. PGx was therefore an area identified for further investigation and is analysed in greater detail in Chapter 5.

Circulating tumour DNA testing

Circulating tumour (ct) DNA testing is a form of genetic testing that makes use of fragments of tumour DNA found in the bloodstream. ctDNA is a form of cell-free DNA, which is released by cells either during cell death or apoptosis, or by secretion. By taking a blood sample, extracting and then sequencing this DNA, clinicians can analyse mutations in a patient's tumour.

With some advantages over conventional solid tumour biopsy, liquid biopsy can contribute to more personalised medicine approaches by:

- Allowing clinicians to sample tumours more regularly and respond to changes in disease course, e.g. measure response to treatment, detect disease relapse or genetic resistance to therapy
- Increase accessibility to companion diagnostic testing and to targeted therapy: a blood sample can be collected when a solid biopsy is not possible due to tumour location, or when a patient is too unwell for the procedure.
- Liquid biopsies are also simpler, safer and less demanding procedures than solid tumour biopsies and do not require a specialist appointment. This means that genetic tests can be carried out more regularly, which in most cancers is not possible using solid biopsy due to the expense and invasiveness of the procedure, and the risk of side effects. In the longer term, liquid biopsy could be used as a screening and early detection tool.

What is the status of ctDNA health applications?

Companion diagnostic ctDNA testing to inform treatment selection

Companion diagnostic ctDNA testing is already available in a small number of NHS laboratories to test for epidermal growth factor receptor (*EGFR*) gene mutation status in patients with non-small cell lung cancer (NSCLC), to determine if they are eligible for targeted tyrosine kinase inhibitor therapy. Testing is available at diagnosis and also when resistance have developed to first line therapy.

Although testing is available in the NHS via a select number of laboratories not all eligible patients receive a test. In terms of implementation the challenges include:

- Engagement about and logistics of testing within the health system
- Support for laboratories to develop tests, mechanisms for test payment
- Lack of guidelines on test use

There is now sufficient evidence in terms of clinical utility to support the implementation of ctDNA companion diagnostic testing in NSCLC [48, 49]. NHS laboratories also cite the technological advances in ctDNA testing, availability of targeted therapy, clinical unmet need and a supportive environment (from clinicians and pharmaceutical companies) as driving test development [50].

While there are some evidence gaps to be filled, which include determining the timing of the test, selecting the most suitable test, and understanding the impact on the overall cost of treating patients, these could in principle be addressed within the next one to three years and are not barriers to adoption of the technology in this context.

Furthermore, the scope of companion diagnostic testing may expand in the near term as testing in other areas and genes, such as *BRAF* in melanoma and *KRAS* in colorectal cancer, are also being investigated by laboratories.

Monitoring for relapse and treatment response, and early detection/screening

Clinical trials are investigating the use of ctDNA testing to direct patients onto clinical trials for targeted therapy [51], and to monitor patients after they have had surgery to remove their tumour [52]. While these areas are promising there is not yet sufficient evidence of clinical utility to support their implementation into the health system. Similarly the use of ctDNA testing for early detection and screening is unlikely within the next one to three years. Reliable detection of early stage cancers is still challenging [53] and further research is needed to determine whether ctDNA is a reliable indicator of early stage cancer.

More broadly future clinical use can be supported by ongoing research and data collection, to determine for example: the optimal strategy for sampling ctDNA for monitoring purposes; clinically relevant somatic tumour variants; the utility of different sequencing approaches for ctDNA analysis. Genomics England are carrying out pilot studies with Inivata and ThermoFisher to determine if ctDNA is a reliable medium for WGS, and in the longer term the clinical utility of ctDNA WGS services.

Summary

ctDNA testing is a fast evolving and clinically useful technology which has a strong research base and is an area of interest to the pharmaceutical industry. Given the availability and clinical utility of ctDNA testing for treatment selection currently for NSCLC, and the likely expansion to other cancers within one to three years, this area will be explored in greater depth in Chapter 5. As there is not currently sufficient evidence to support the use of ctDNA testing to monitor relapse and treatment response, and in early detection and screening, these areas were not taken forward.

Microbiome analysis

An enormous collective community of different micro-organisms (microbiota), such as viruses, bacteria, and forms of fungi live in and on the human body. The microbiome is a term used to refer to all of the genetic material within a microbiota (i.e. collection of microorganisms present at particular sites), for example the genomes of all microorganisms in the gut are referred to as the gut microbiome. Increasingly the term is also being used to refer to the analysis of small molecules and metabolites produced by the microbiota.

Microbiome analysis may be restricted to particular organisms within the sample or applied to the whole sample, and can also be restricted to particular genes or transcripts, or extended to all the RNA (metatranscriptomics) or DNA (metagenomics) within a sample. Microbiota have functions that are conserved across individuals and play an important role in number of processes including metabolism and the development of the immune system [54, 55].

Microbial dysbiosis (imbalance) has been linked to a wide variety of diseases and given its dynamic nature, changes in its composition or function may be indicative of disease development. Detailed analysis of the microbiome and its manipulation in individuals has the potential to enable a more personalised approach to prevention and treatment. Since the microbiome is unique to individuals it may also potentially serve as a source of novel biomarkers that are more 'person' specific.

What is the status of microbiome analysis based health applications?

The analysis or therapeutic use of the microbiome is currently predominantly in the pre-clinical research phase, with no advanced applications that involve molecular analysis of the microbiome being developed within clinical settings.

General approaches to microbiota manipulation as a therapeutic strategy is practiced to some extent, including faecal microbiota transplantation (FMT) for severe cases of recurrent *Clostridium difficile* infections, and the use of pre-, pro- or synbiotics to either replace or promote growth of particular microbiota species. Many of the current approaches used are crude and the mechanisms by which they work are not clearly understood, additionally they require further study to validate initial findings [56].

In the future as knowledge about the microbiome increases, it is hoped that more precise manipulation of the microbiome may become possible by manufacturing microbial communities in the laboratory or engineering specific microbes to aid in metabolic processes or through better fine-tuning of dietary supplements through identification of the metabolites that microbiota produce within the body. There is a huge interest from pharmaceutical companies and biotechnology firms in the development of microbiome-derived therapies and this is an area of increasing investment.

Continuing advances in 'omics technologies and computational methods have transformed the capacity to investigate microbiomes and made this a highly active research area [57, 58].

Changes in the microbiome have been associated with a number of diseases such as Crohn's disease [59, 60], diabetes [61] and conditions such as obesity [62] where it has been shown that host genetics together with the gut microbiota have an impact on metabolic phenotypes. Gut microbiomes have also been shown to impact on the efficacy of drugs [63–65], which may explain varied drug responses between individuals.

Currently the clinical translation of these findings is challenging because:

- It is unclear whether changes in the microbiome are causal or as a result of disease
- The dynamic nature of the microbiome – with variation between individuals, between two sites in the human body and over time – makes analysis complex
- Microbiomes interact with each other, their hosts and the environment which can lead to difficulties in developing the underpinning knowledge base to identify and characterise them

Consequently microbiome analysis is still an arduous and complex task that involves investigation of a large volume of data, and much of the microbiome remains poorly understood.

Greater knowledge of the microbiome is fundamental to better understanding what changes in microbiota indicate, identifying and validating biomarkers [57, 58], and ultimately developing clinically useful applications. Equally, greater collaboration between health professionals and research scientists may help to identify particular clinical contexts and applications for which microbiome analysis would be useful. There are many efforts underway to ensure that progress is made in this field through interdisciplinary research, sharing of data and skills and expertise.

Summary

Microbiome analysis is widely regarded as an important component of personalised medicine due to the difference between individuals, communities and populations. The large body of research in this field is likely to lead to the development of precision healthcare applications in the future. As there are no applications of this technology (beyond FMT) currently close to clinical implementation, microbiome analysis was not shortlisted for further analysis in this report.

Single cell 'omic analysis

Single cell analysis (SCA) is the application of 'omics technologies – genomics, proteomic and transcriptomics – to an individual cell, as opposed to whole populations of cells or tissue samples. Special techniques are used to isolate individual cells before DNA, RNA or proteins are extracted for analysis: so the material analysed is specific to an individual cell.

There is a high degree of heterogeneity between cells of the same type, this stems from variability in intrinsic cellular factors e.g. mutation, differences in gene regulation as well as extrinsic factors such as environmental challenges and how individual cells respond to these. This variability has an influence on individual cell fate and consequently can impact on disease development and progression. A classic example of this is cancer, where a single cell can evolve and lead to the formation of a malignant tumour, itself composed of a heterogeneous population of cells. Profiling tissues or tumours at the population level can mask intercellular variations that can be functionally or clinically relevant.

The ability to analyse individual cells in high-definition can facilitate personalised medicine approaches in three main ways:

- By allowing precise molecular differentiation between cells that are pathogenic or 'normal' at the cellular level (e.g. those isolated from embryos), thereby enabling more precise therapeutic interventions
- By allowing identification of rare events and rare cell types associated with disease (e.g. cancer or microbial cells), information which may enable greater precision in disease identification
- As the technique is applied to a minimal number of cells, it may have practical advantages in screening and diagnosis of disease where there are limitations in the amount of sample available (e.g. non-invasive prenatal diagnosis)

What is the status of single cell analysis based health applications?

Single cell analysis is still very much in the research arena, for two main reasons. Firstly, technical capability to analyse single cells remains in the developmental phase; consequently much of the current research is focused on developing the technologies and robust workflows, including computation methods to analyse raw data [66–68]. Single cell analysis cannot easily be addressed by conventional analytical methods as each cell is measured once, meaning there are no replicates. In addition, there is a large amount of variation in the amount of starting material that is analysed, which makes statistical interpretation difficult. Most currently available technologies for single cell isolation, genomic or transcriptomic analysis and downstream computational methods are still limited in throughput, accuracy and are labour intensive and costly [69].

Secondly, developing clinical applications is limited by current scientific knowledge in relation to single cell biology and its relationship to disease. Promising areas of research are pre-implantation genetic diagnosis (PGD), where single cell genomics could widen the scope of genomic analysis and also enable a generic and standard approach for detection of a number of types of genomic variation.

Cost and the time taken to perform such analysis are current limitations to the use of sequencing at the single cell level for PGD [70, 71]. Studies have also demonstrated the application of SCA to circulating fetal cells for non-invasive prenatal diagnosis (NIPD). The pace of development of this analysis is dependent on progress made in reliable isolation and analysis of rare fetal cells present in maternal blood [71]. Once this is overcome, it has the potential to replace current methods for NIPD.

Similarly, building on current methods to analyse cell free tumour DNA, attempts are being made to analyse single tumour cells, either circulating in the blood or from solid tumours to aid early detection, diagnosis and prognosis. Apart from overcoming technical hurdles in consistent isolation and analysis, the clinical validity and utility of using this approach has yet to be demonstrated [71, 72].

Summary

Single cell analysis offers the opportunity to obtain unprecedented levels of information into the molecular characteristics of disease at a level of resolution not previously possible. However, most clinical applications, including single cell 'omics analysis for the assessment of human embryos prior to implantation, are still very much in their infancy. Whilst clearly a powerful tool for advancing future personalised medicine approaches, single cell analysis was not shortlisted for greater analysis in this report at this stage.

Pathogen genomics

Whole genome sequencing (WGS) gives the highest possible resolution information possible about the genetic sequence of pathogenic organisms. In the context of personalised medicine this information could be used to:

- More accurately prescribe antimicrobial therapy where genetic determinants of antimicrobial resistance (AMR)/susceptibility are known
- More accurately and rapidly determine the cause of outbreaks (e.g. within a hospital setting in situations where conventional infection control methods are not working). This allows a hospital to put better informed and targeted infection control policies in place
- Carry out surveillance of pathogenic organisms. This will allow a health system to respond to outbreaks as they emerge and also to target the source(s) of outbreaks to prevent further transmission

What is the status of pathogen WGS applications?

Currently there are two key areas where pathogen WGS could have an impact within a three-year time frame: the management of tuberculosis and outbreak management in the healthcare setting.

Pathogen WGS: tuberculosis

Tuberculosis is the only disease for which WGS has demonstrated clinical utility in several different applications of pathogen WGS including: diagnosis, surveillance, outbreak detection, and antimicrobial susceptibility/resistance testing to inform drug prescribing.

Currently tuberculosis WGS is carried out by Public Health England (PHE), and while there has been little change for the NHS in terms of submitting samples to PHE, there has been some changes in the information returned to the NHS by PHE, although all sequence data remains within PHE. In the future, technological advances such as culture-free and portable sequencing could have an impact on tuberculosis management; sequencing could be undertaken in different locations and closer to patients. This may raise the need to consider the dynamics of data flow between organisations in order to meet both clinical and public health needs.

Pathogen WGS: Outbreak management in hospitals

WGS is recognised as a useful tool for outbreak management of a range of pathogens and is already used by PHE in the management of large-scale outbreaks, which are their responsibility (e.g. *Salmonella* food poisoning [73]). A policy document from the European Centre for Disease Control and Prevention recommends that WGS is used for outbreak management, particularly for food-borne disease [74]. The use of WGS has also been shown to contribute to the resolution of disease outbreaks in a hospital setting [75, 76]; an area typically outside the remit of PHE (unless the outbreak is of a notifiable disease or pathogen).

However the use and uptake of WGS in the hospital setting is dependent on local expertise and access to sequencing, raising the question of if and how the wider NHS may undertake or access pathogen sequencing for this application.

Antimicrobial resistance management

Using WGS to determine antimicrobial susceptibility or resistance can in principle replace multiple phenotypic tests with one test/assay. While molecular typing is provided by PHE laboratories to supplement phenotypic assays and there is evidence of utility in using WGS in AMR surveillance efforts [77], there are evidence gaps as to its use as a clinical tool for AMR testing. This is because for most pathogens there is currently insufficient knowledge of the correlations between genotype and AMR phenotype. Also most phenotypic tests are cheaper and take less time than sequencing.

As the cost and time of sequencing continues to drop, there is much potential for genomics to inform AMR management. Future use could be accelerated by supporting development and curation of reference databases of AMR genes. In the short to medium term, point of care genotypic or phenotypic assays currently in development show more promise for determining antimicrobial susceptibility.

Summary

Pathogen genomics is enabling the more targeted management and control of infectious diseases and transforming the delivery of microbiology services.

There is a growing body of evidence that genomics can be used for outbreak control and could in principle be applied to any pathogen. There is a firm evidence base and established public health services using WGS for tuberculosis management spanning diagnosis, outbreak/surveillance and drug treatment decisions. As such these applications were shortlisted for greater analysis.

In contrast, the use of WGS for AMR management is still under development for most pathogens – and first requires the curation of accurate, comprehensive databases of genotype-phenotype correlations. Therefore this topic was not taken forward for greater analysis in this report.

3.2 Supporting the clinical advancement of 'omics technologies

Each of the 'omics technologies described in the preceding section possess their own unique technical challenges, reflected in part by the differing extents of their clinical translation. At the same time there are a number of common themes that apply across all of these technologies and their applications. Irrespective of their current-state of clinical readiness, maximising the future utility of 'omics analyses for personalised medicine requires some degree of system preparation in the near term, particularly across these cross-cutting areas.

Cross-technology coordination

Whilst we have reviewed each 'omics technology individually, the molecules they measure are intrinsically linked and their biological functions interdependent. Viewing these collectively, rather than in isolation will provide a better understanding of molecular mechanisms underpinning disease and in turn more targeted diagnostic or therapeutic strategies. This will rely on:

- Coordination of activity across 'omics platforms to enable holistic insights into disease processes, and to capitalise on opportunities to share common infrastructure
- Integration of 'omics data and knowledge across multiple sources

Data management: analytics, sharing, security and storage

High throughput 'omics technologies generate vast volumes of data, of a scale and complexity not previously encountered within the context of routine health services. Data management strategies for 'omics data are essential to the deployment of these technologies, including:

- Data storage solutions and computational resources – 'omics based analyses consume significant storage and computational power
- Sharing and pooling of data, including clinical information – to support accurate data analysis
- Data security measures and processes to manage patient confidentiality – especially for linked data sources (e.g. genomics or metagenomics data combined with clinical data) that might be identifying
- Analytical approaches for large, complex, high-dimensional datasets – for initial knowledge discovery but also to deliver future clinical analysis

Standards and harmonisation of practice

'Omics technologies and 'omics data analyses are dynamic and continue to evolve. Given the state of rapid change maintaining flexibility to adopt new techniques that present improvements in accuracy and performance is necessary. At the same time, it is essential to seek opportunities to standardise experimental techniques and harmonise analytical approaches as methods become more established; for example, in raw sample preparation where variation can be a significant source of systematic and one-off errors.

Harmonisation of practice can help research and discovery and future clinical use to progress by:

- Establishing quality control and standards
- Ensuring datasets generated across centres are comparable
- Ensuring findings are robust and reproducible

These cross-cutting areas will be explored further in Chapters 4 and 5.

3.3 Technologies that enable more personalised therapeutic interventions

Here we review a range of technologies that are enabling treatments and interventions tailored to the individual characteristics of the patient.

Some of these interventions are being informed by the detailed molecular characterisations of patients (e.g. genomic information leading to targets for gene therapy and gene editing); others are being driven by advances in imaging and digital technologies (e.g. 3D printing and robotics).

In all cases these technologies make a considerable move away from one size fits all therapies to highly specific interventions.

Stem cell therapy

In adults, stem cells play a role in tissue repair and regeneration. They are cells that are able to differentiate into a number of different cell types, for example stem cells in the bone marrow differentiate into all the different cells found in the blood: immune cells, red blood cells and platelets.

Broadly, stem cell therapy is any healthcare procedure that targets stem cells or utilises them as a medicinal product. Stem cells are increasingly being used for cell-based therapies because of their ability to self-renew and to differentiate into specialised cell types.

Stem cells can either be obtained from developing embryos or adult tissue; however, the vast majority of treatments utilise adult cells. Depending on the origin of adult cells, stem cell therapies can be categorised as autologous (from the patient) or allogeneic (from a donor, usually a close relative). Autologous treatments are becoming more common for both rare and more common conditions as they help to avoid complications such as graft versus host disease associated with donor cell therapies, and are highly personalised in the sense of making use of the patient's own cells.

Some stem cell therapies have been in common use for decades. These include haematopoietic stem cell transplantation (HSCT) – i.e. bone marrow transplant – to treat myeloma, leukaemias and lymphomas, and skin stem cells for skin grafts. In recent years other stem cell therapies have emerged, including those used in combination with gene therapy or gene editing (next section).

What is the status of stem cell therapy health applications?

Beyond established treatments, there are a number of novel stem cell applications in research and development, including in the treatment of diabetes and in the treatment of radiation wounds [78, 79], and a select few in clinical use. Novel therapies that utilise stem cells and novel uses of conventional stem cell transplants are beginning to impact health outcomes of rare conditions in small numbers of patients. There has been notable progress in the advancement of combined stem cell and gene therapies for blood disorders such as β-thalassemia and sickle cell disease.

There are currently two NICE approved stem cell-based Advanced Therapeutic Medicinal Products (ATMPs) available for use in the UK. Holoclar was Europe's first approved stem-cell based ATMP, and is available through the NHS for the treatment of eye burns. Subsequently Strimvelis, an *ex vivo* gene therapy that targets stem cells, was given marketing approval by the European Medicines Agency (EMA) in 2016 and is available on the NHS for the treatment of Adenosine Deaminase specific Severe Combined Immunodeficiency Disorder (ADA-SCID), for which there is no other curative treatment. Stem cells are also in use in tissue regeneration beyond standard treatments, such as in autologous stem cell enriched fat grafts used in breast reconstruction surgery following cancer treatment [80].

Despite the growing number of clinical trials and two ATMP approvals, the availability of treatments for some rare disease remains limited to trials. In addition, clinical trials and treatments often have small patient numbers, so there is a lack of large-scale long-term evidence relating to treatment efficacy, patient outcomes, and safety for some applications.

There are several system implementation challenges, some of which are being addressed through existing initiatives. These challenges include logistical difficulties in transportation, storage and handling of live cells for therapeutic use; the need for high-spec treatment units; and the high cost of some therapies [81]. Both near-term and long-term planning for these challenges is necessary to ensure that as the number and scale of therapies increases, the heath system is responsive to their adoption.

Summary

There has been recent accelerated progress in the development of stem cell therapies and regenerative medicine more generally; individual therapies are at differing stages of development, and new therapies are emerging with some frequency. Novel treatments that utilise mature stem cell techniques and infrastructure, such as HSCT for multiple sclerosis, are likely to advance at a greater pace than more complex therapies such as combined gene and stem cell approaches for some rare diseases.

Regenerative medicine (RM) is an important strategic area within the personalised medicine landscape, with significant investment due to be made in advanced therapy treatment centres and industries complementary to RM. Given the need for longitudinal planning to support the future adoption of these therapies, this area along with gene therapy and gene editing is reviewed in Chapter 5 in greater detail under the heading 'Regenerative medicines'.

Gene therapy and gene editing

Gene therapy and gene editing utilise advanced clinical techniques to alter the genetic information of a patient's cells. This may extend to integration of new information into the patient genome, deletion/alteration of part of the genome or simply insertion of new information into the cell.

In some instances 'gene therapy' is used as an umbrella term for all gene-related treatments, including gene editing, and the terms are often conflated and can be inconsistent across various information sources. A distinction can be drawn based on the mechanisms utilised during therapy i.e. viral vectors for gene therapies or specific gene editing tools (ZFNs, TALEN and CRISPR) used in gene editing.

Gene therapies (including gene editing) offer the potential to treat conditions that are currently without any curative treatments, complementing the broader application of genomics-based diagnostics. Therapies can include editing of the patient's own genetic information, meaning treatment is personalised to a high degree.

What is the status of gene therapy and gene editing health applications?

Recent advances in gene therapies have revealed several highly promising applications of these techniques, although many are in early stages of development. Somatic cell gene therapies for blood disorders such as haemophilia and sickle cell disease, cancer treatment, incurable immuno-deficiency, and retinal disorders have made significant scientific or regulatory progress in the last few years.

Germline editing remains research-only as there has been a moratorium on germline editing for several years, with the first permissions for embryonic editing for research in the UK given in 2016. The use of gene editing *in vivo* is at the very early stages of human and animal trials [82].

Gene therapy for the treatment of rare diseases and cancer

International development of gene therapies has been slowed by safety concerns and regulatory complexity. In the last few years major progress in the clinical application of these technologies has become evident. Emergent techniques, such as lymphoma treatment using chimeric antigen receptor (CAR)-T cells, hold substantial promise in the treatment of a number of related conditions. This therapy involves extracting a patient's T-cells, genetically modifying them to express antigen receptors on their surface and then infusing them into the patient – it is a truly personalised therapy as it uses the patient's own immune cells.

Other forms of CAR-T therapy under development aim to create an off-the shelf product using donor cells. CAR-T therapies are currently in clinical trials and two have received FDA approval,with further work needed to confirm clinical effectiveness and safety.

CAR-T therapy is a maturing technology area, presenting new opportunities in cancer therapeutics. Although wide-spread adoption may be challenging, and some concerns surrounding adverse effects post-treatment need to be addressed, some of these technologies are expected to gain European Medicines Agency approval within the next one to three years. The implementation of approved therapies will place high demands on infrastructure, training, skills, and resources.

Inherently small scale rare disease trials have showcased the promise of gene therapies, for example, in the form of a potentially curative treatment for haemophilia A [83]. In some cases these therapies may alleviate the need for long-term routine medications or treatments for patients. In the long-term they may also represent cost-saving for the healthcare system as prospective one-off treatments for chronic conditions. The first instance of live (*in vivo*) gene editing in a human was carried out on a single individual in the US in late 2017. Gene editing therapies are attracting substantial investment internationally, and are being refined to improve their specificity and efficacy. Long-term follow up and testing for each specific application needs to be conducted on a number of patients to ensure the safety and efficacy of the technique.

There are several challenges that currently limit the broader clinical utilisation of gene therapies and gene editing. The scope of application for gene therapies is limited in part by knowledge of the genetic causes of disease; currently, monogenic diseases (with a known single genetic cause) represent the most promising clinical targets.

In addition, gene therapies can consume a lot of time and expense to develop and, although many of the tools utilised are common or similar across a range of conditions, they need to be adapted for each specific purpose (e.g. targeting of a specific gene, tailoring of viral vectors for each insert) and require extensive testing to ensure acceptable specificity and efficacy. Curating a sufficient evidence base for approval of these therapies in rare disease is challenging due to small patient numbers and long follow up required.

Summary

There are an increasing number of powerful exemplars of gene therapies, especially within monogenic and haematopoietic disorders. Although further treatments will emerge within the next three years and several treatments are being trialled in patients, the large-scale implementation of many diverse and high complexity treatments within clinical services is not expected in the next one to three years due to technical and practical challenges related to the clinical adoption of technology. As with stem cell therapies, gene therapy and gene editing are essential elements of regenerative medicine – a key strategic area within the personalised medicine landscape with a specific requirement for longitudinal planning. This area was therefore raised for further review in Chapter 5 under regenerative medicines.

Virtual and augmented reality

Virtual reality is a computer-generated simulation that immerses the user in an artificial experience by stimulating their vision and hearing. In contrast augmented reality is the bridge between the 'real' and artificial world, where computer-generated enhancements are layered atop existing reality. In both systems the user is able to interact with the virtual or augmented world that simulators create.

Although virtual and augmented reality (VAR) programmes are predominantly developed by the commercial gaming industry, more recently, due to the highly adaptable nature of VAR, applications for healthcare are emerging to engineer realities that deliver therapy or help diagnose disease. Dementia, mental illness and rehabilitation are just some of the areas of clinical or research developments applying VAR.

What is the status of virtual and augmented reality health applications?

Therapeutic interventions for anxiety disorders, stroke rehabilitation and pain management

Promising applications of VAR are in treating mental illness and phobias; in the latter case by exposing the patient to the source of fear in a controlled virtual environment. Following a successful NHS trial, a virtual reality system – known as the Blue Room – for the treatment of phobias in children with autistic spectrum disorder is now available on the NHS. There are a number of other VAR programmes to target therapy for managing depression or anxiety, but these have limited evidence or trials of significant duration demonstrating superiority over standard interventions.

Various clinical trials for augmented reality programmes are underway, for example reducing pain caused by injections for children with cerebral palsy [84] and gait adaptation for stroke patients [85]. However the magnitude of effectiveness compared to standard, lower cost treatments still needs to be established. Given their clinical use is currently very limited and evidence is still being established, these applications of VAR are unlikely to present as significant system requirement in the next one to three years.

Surgical planning and training

There have been trials in surgical specialties examining the use of VAR to assist with planning or undertaking surgery. By using VAR to simulate the internal organs of a patient, surgeons can practice and plan out surgery more precisely. VAR simulations are also being explored as medical training aids. The effectiveness of these techniques over existing or emerging alternate approaches e.g. surgical planning and training using 3D printed anatomical models, has yet to be demonstrated.

Broadly the main limitations for the application of VAR technologies include:

- The lack of large validation studies and comparison to alternative methods of practice
- The overhead cost of equipment – at a time where the technology is rapidly evolving and improvements in hardware are underway
- The extensive technical expertise required to create effective and immersive simulations, as well as expertise to run and tailor programmes for individual patients.

The most advanced applications of VAR technology are likely to emerge through intersection with other technologies including medical imaging, 3D modelling, robotics and AI. These interactions could provide remote care options and more tailored therapy and diagnostics.

Further development of VAR towards broader clinical utility could be supported by encouraging collaborations between clinicians and VAR developers to inform and identify rational solutions to clinical need. Furthermore the future regulation and guidance on validation of VAR approaches may need to be considered. This is because of the increasingly blurred boundary between approaches that might be considered medical devices and those that are lifestyle applications.

Summary

The medical use of VAR is likely to evolve as technology hardware developments in headsets and 3D imaging and 3D glasses advance. Due to the limited evidence of clinical utility and benefits over standard procedures or other available technology applications, the few emerging applications of VAR were not considered for greater analysis in this report.

3D printing

Three dimensional (3D) printing, also known as additive manufacturing, rapid prototyping and solid free-form technology, is a manufacturing process used to create customisable objects by depositing or binding successive layers of material. Computer aided design (CAD) files or other image files (created by scanning an object) instruct the 3D printer of the shape of the object. For some applications, 3D printing can be viewed as an extension of advanced image analysis, whereby 3D rendered models can be created by using medical images (e.g. MRI) and converted into digital 3D print files to create bespoke devices and models.

There are many different 3D printers with varying technologies, speeds, resolutions and materials (e.g. metals, plastics, ceramics, powders, and living cells). The greatest advantage of 3D printing for medical applications is the ability to customise devices and implants for individual patients.

What is the status of 3D printing health applications?

Personalised prosthetics, orthotics, implants, anatomical models and surgical guides

The most common 3D printing applications for healthcare are surgical guides, anatomical models, and custom implants [86], with research activities largely focussing on craniofacial, oromaxillofacial, and cardiothoracic specialties [86]. Anatomical models can be created to allow surgeons to plan and simulate surgery in advance of complex procedures. They are expected to reduce operation time and post-operative complications [87, 88].

Cost is influenced by the type of printer and material used, the application and the type of surgery [86]. There is a lack of systematically collated cost-benefit evidence, although, some commercial companies claim reductions in procedural costs where 3D printed models for pre-surgical planning are used [89].

Personalised implants may benefit patients where a standard implant does not exist or a one size fits all implant may not be suited to the patient's anatomy. There is a growing body of evidence that 3D printed implants reduce surgery times and improve patient outcomes across a variety of surgical specialties, including cranio-maxillofacial [90, 91], thoracic [92], spinal [93], and orthopaedic [94–96].

Clinically trialled personalised orthotic insoles are already available on the NHS, however, other 3D printed orthotics, such as knee braces, are still under clinical trials. Various direct to consumer and crowdsourced initiatives exist in the United States for users to obtain or print their own bespoke prosthetics [97, 98] including a National Institutes of Health platform. In the UK a clinical trial of 3D printed bionic hands for children is underway at North Bristol NHS Trust in collaboration with the company Open Bionics.

3D printing adoption is occurring in other healthcare systems including Germany, Australia and the United States, where the FDA has recently developed technical guidance for additive manufacturing devices in response to burgeoning activity.

In England a number of hospitals and their clinicians are already engaging with this technology with some having access to 3D printing services by hospital owned or in house commercial providers. However, current use is fragmented and inconsistent between and within hospitals and typically dependent on physician awareness, reimbursement processes, as well as access to the appropriate infrastructure and skills e.g. imaging and modelling software, 3D printers and digital infrastructure.

Printing of live cells (i.e. bioprinting) for tissue repair and replacement

3D bio-printing is anticipated to transform regenerative medicine by enabling the printing of personalised organs and tissue. This field is still very much in its infancy. Early studies have demonstrated proof of concept for fabrication of organ and tissue for regeneration and the use of 3D printed biotissue for pharmacological investigations is being explored. Many technical barriers to clinical translation remain, such as building tissue connected by vasculature and fabricating complex biological structures [99].

Bone and cartilage printing is a promising area; advances include a handheld stem cell 3D printing BioPen device for cartilage regeneration [100] and printing of cartilage tissue using stem cells [101]. However, feasibility in humans remains to be demonstrated. A nearer-term application is the use of customised implants seeded with stem cells, to limit implant rejection or encourage tissue regeneration [102].

Future clinical capabilities of 3D printing will be facilitated by advances in material science, printing technology, and medical imaging.

Summary

3D printing and the underlying 3D imaging technology is enabling the detailed characterisation and modelling of an individual's anatomy for highly personalised therapeutic interventions. Whilst the printing of live cells is still in early stages of development, 3D printing of implants, anatomical models, and to some extent prosthetics is more advanced and implementation is occurring in some parts of the health system. Considering this together with the growing evidence for improved patient outcomes, 3D printing of implants and models was shortlisted for review in greater detail in Chapter 5.

Robotics

Robotics is an interdisciplinary field that includes mechanical engineering, electrical engineering, and computer science. Broadly robotics technologies are used to develop machines that can replicate, substitute, or enhance human tasks by processing information and providing feedback.

Developments in robotics most relevant to personalised medicine applications include systems that facilitate greater surgical precision and robotics for therapy and rehabilitation.

What is the status of robotics health applications?

Robotics assisted surgery and therapeutics

Applications for surgery include a minimally invasive robotics tool that allows surgeons to perform normally invasive, complicated procedures through just a few small incisions.

One tool, the da Vinci System, has been found to shorten hospital stays, decrease complication rates and allow surgeons to perform more precise tasks [103]. The initial investment in the system ranges from $1 million to $2.5 million. Studies indicate cost-benefit outcomes can vary depending on the surgical procedure being conducted [104].

Whilst robotics assisted surgical systems are already in use across a number of hospitals in England, reviews by specialised commissioning have concluded to not routinely commission some robotics assisted surgical procedures due to a lack of evidence in support of clinical effectiveness [105–108].

Other applications of robotics include tissue classifying surgical tools such as the iKnife and SPIDERMASS, which analyse vaporised lipids by mass spectrometry to assist in distinguishing diseased tissue from non-diseased tissue during a surgical procedure.

Researchers and surgeons at Imperial College London have been trialling the iKnife for brain, breast, colon and ovarian cancer surgery since 2014. Proof of concept studies for the iKnife have been conducted for several tumour types *ex vivo* [109] and intraoperatively [110]. However further validation studies are required to determine the accuracy for intra-operative use [110].

Ambulatory exoskeletons such as H2 and Ekso have been designed to aid patients with difficulty manoeuvring following injury or disease e.g. stroke, by tailoring movements to their specific needs (gait training). The ultimate aim of this technology is to assist patients in regaining as much of their natural gait as possible. A NICE Medtech Innovation Briefing on the use of the Ekso exoskeleton for rehabilitation in people with neurological weakness or paralysis noted the evidence base is currently very limited and the resource impact is unclear [111].

Broader applications of robotics in healthcare including robotic medical assistants are still evolving and the pace of developments will be influenced by advances in other areas particularly artificial intelligence, electronics, and nanotechnology.

Since the robotics industry is rapidly growing, it is likely that the capabilities and performance of robotic technologies in healthcare will improve in the future to provide for more compact and possibly less expensive assistive technology than currently available. Future developments could be facilitated through collaborations between robotics developers and clinical end users.

Summary

Robotics is a rapidly evolving field, with healthcare applications likely to widen particularly as robotics is combined with other technologies including artificial intelligence. However, for existing applications of this technology, the evidence-base is still being generated and is unlikely to be concluded in a time frame to support widespread adoption in the next one to three years, therefore, robotics applications were not shortlisted for further analysis in this report.

3.4 Supporting the clinical advancement of personalised therapeutic interventions

Personalised therapeutic interventions reviewed in the preceding section are diverse and range from those that operate at the molecular level (gene editing) all the way to the morphological level (3D printed implants). Many of these technologies are converging, for example stem-cell seeded 3D implants. Across this range of personalised therapeutics, the common recurring priorities for facilitating the clinical impact of these technologies include:

- Cross-discipline and cross-sector collaboration to strengthen and produce knowledge to inform therapeutic strategies. This is relevant given that the most transformative interventions are emerging through the convergence of different technologies, and to help inform the development of medical applications for the range of technologies initially arising in other non-biomedical sectors (e.g. VAR, or 3D printing)
- Innovative trial designs and analytical and statistical approaches for quantifying effectiveness in low number trials. The upshot of more targeted therapeutic interventions that are applicable to a smaller and smaller pool of patients (in some instances n of 1) is the challenge in investigating and demonstrating safety and clinical efficacy
- Harmonisation and clarity around regulatory requirements for personalised therapies and interventions, including evidence requirements, and definitions applied for the regulatory classification of therapies and devices
- Developing appraisal methodology to better address key challenges for new technologies

3.5 Underpinning and enabling 'bioengineering' technologies

The preceding sections describe the existing, emerging or potential future applications of a range of technologies. The personalisation of medicine is also being driven by advances in particular approaches that transform the performance and capabilities of other technologies. The bioengineering approaches outlined below may not directly personalise healthcare in and of themselves, but may underpin developments in other biomedical technologies and clinical devices in ways that facilitate the development of personalised medicine approaches. In particular these technologies complement and will have an impact on the development of applications that allow more personalised disease monitoring such as point of care devices and wearable sensors (Chapter 4). Underpinning digital and data analysis approaches are also discussed in Chapter 4.

Microfluidics

Microfluidic technologies aim to miniaturise standard laboratory processes into portable or handheld devices. At the core of these devices are microfluidic chips which allow for the movement of fluids in very small spaces. Channels and wells within the chip(s) allow fluid mixing in a controlled way such that chemical reactions can take place on the micro-scale. Any device containing microfluidic technology also requires accessory equipment to deliver and control the flow of fluid through the chip and also measure or analyse any results. As such, the use of microfluidics is not just limited by what is possible within a chip, but also what other equipment is needed to make the device function. The greatest impact of this technology will be within hand-held or point of care devices, or in single-use devices made of paper or cloth that will have their impact in low-resource health systems.

The application of microfluidics is not universal in that the so called killer application, a technological advance which allows the universal miniaturisation of laboratory processes, has not yet been found. Therefore application of this technology is currently on a case-by-case basis. One example of a point of care device using microfluidics is the Abbott i-STAT analyser which has been tested in trials to measure blood lactate which is a marker used to identify patients at increased risk of mortality from sepsis.

Nanomedicine

Nanotechnology encompasses the design and production of structures, devices and systems at the nanoscale (objects that are measured in nanometres, or billionths of a metre), while nanomedicine is the novel application of nanotechnology in a clinical context. The four areas where nanomedicine has the greatest potential are i) delivery of pharmaceuticals; ii) diagnostics; iii) regenerative medicine (materials for cell therapy) and iv) implantable devices.

Examples of nanomedicine in practice include nanoparticles or liposomes containing drugs to facilitate targeted drug delivery, particularly in cancer. This type of application is relatively simple in that it facilitates a certain clinical process, but does not further personalise treatment according to the features of the patient's disease. Currently, truly personalised nanotechnologies are far from commercialisation, let alone routine use.

Synthetic biology

Synthetic biology involves applying engineering design principles to biology, to design and construct novel biological functions or systems where they do not exist, as well as redesigning existing biological systems for useful purposes. It is a form of genetic engineering: biological parts – sequences of DNA that code for basic biological functions – are put together in ways that do not exist in nature. These parts can be derived from existing organisms or synthesised from scratch. Parts are combined to create devices that perform a useful function, such as a transcriptional switch. Many devices can be combined in a host organism to create a system that can carry out a more complex function, such as a biosensor. An early success of synthetic biology was the branched DNA assay, invented in 1997, which is now used routinely to measure viral load for HIV and hepatitis C virus.

One area where synthetic biology could have an impact in personalised medicine is via theranostic devices, which are designed to detect biomarkers relevant to a specific disease and then couple this to the production of a therapeutic response e.g. an immune system response to treat inflammation. Theranostic devices have been investigated in animal models of metabolic disorders with promising results however there is currently minimal evidence of their effectiveness in people.

Synthetic biology shows promise in the development of targeted cancer therapy, specifically chimeric antigen receptor-based (CAR) T-cell immunotherapy (Section 5.4). For all synthetic biology applications, a fundamental knowledge of molecular processes is needed, as well as understanding safety issues and mitigating against them (safety by design).

3.6 The challenges for the implementation of bioengineering technologies

Common issues affect the use and integration of bioengineering technologies into the clinical application of other technologies. These include:

- Scientific and technological barriers such as reproducibility and quality control of the technology/device
- Manufacturing challenges such as high production costs, conditions needed for manufacture (e.g. stringent clean room conditions), cost of materials, ability to scale-up production
- Incorporating the technology into devices (e.g. miniaturising accessory equipment for microfluidic devices)
- Optimisation of the technologies for maximum therapeutic potential
- Lack of knowledge on health and environmental impact, and safety concerns, particularly surrounding the use of nanotechnology
- Specificity of the technology/device, particularly if it is used to contribute to delivery of targeted interventions. It is important to avoid off-target effects of a technology.

Advancing bioengineering technologies into clinical applications

As the technologies described here evolve, they could have a transformative impact on the delivery of personalised medicine, particularly through the use of devices that diagnose and monitor disease.

The development and integration of bioengineering technologies into personalised healthcare could be accelerated by:

- Continued support for the basic research required to drive improvements in devices and techniques, for example material science and miniaturisation
- Broader policy engagement and strategies to support technology development, manufacturing and application to medicine. Existing exemplars include manufacturing initiatives for regenerative medicine (Section 5.4) and the Government established Synthetic Biology Leadership Council to set out a clear vision for and support developments in synthetic biology

The impact of the digital revolution

Our capacity to generate 'omics data has outstripped our ability to manage, analyse, and interpret it. The pace and scale at which we can derive novel insights to inform personalised medicine is inextricably linked to the digital and analytic solutions available to harness data.

This chapter sets out the key drivers for, and requisites to, harnessing health data and digital tools for personalised healthcare. These include:

- The critical underpinning digital infrastructure required for personalised medicine
- The growth in digital technologies enabling personalised disease monitoring
- The transformative potential of artificial intelligence and machine learning for data analytics

4.1 The essential role of digitisation of healthcare and health information

Data and digital infrastructure are essential to support the effective clinical utilisation of all of the technologies covered in this report. Our capacity to generate 'omics data has outstripped our ability to manage, analyse, and interpret it. The pace and scale at which we can derive novel insights to inform personalised medicine is inextricably linked to the digital and analytic solutions available to harness data.

In addition to high-throughput 'omics technologies, enormous volumes of health-related data are now generated through handheld or portable digital tools, wearables and mobile devices, and digitally enabled sensors. Some of these digital devices are designed for use within the health system, while a significant number are direct to consumer in nature.

In both instances these digital tools offer an unprecedented opportunity to monitor patient health and disease in greater detail than has been previously possible. The information revolution in health is unfolding.

4.2 Establishing the critical digital infrastructure

Personalised medicine fundamentally relies on the successful digitisation of patient records, other healthcare data sets, and increasingly 'citizen generated' health-related data.

Electronic health records (EHRs) are digital records of a patient's health and care that should in principle allow for the rapid, secure and streamlined sharing of information between healthcare professionals. Patient health records are a critical source of information required for the development or delivery of most personalised medicine applications. For example, the clinical information contained within a health record is routinely required to guide the accurate interpretation of genomic data.

The benefits of digitisation transcend the delivery of personalised medicine. EHRs are needed for the delivery of safer, more effective, efficient, and secure healthcare.

Healthcare digitisation

Whilst primary care in England is nearly 100% digitised, EHR adoption in secondary care has been slow and challenging. Upgrading digital infrastructure and digitisation of paper records has been an ongoing ambition of the English health system. Policy in this area is continually evolving. The FYFV set out aims for the NHS to 'exploit the information revolution' with specific goals for the health system to go paperless by implementing fully interoperable EHRs, and for citizens to be able to access and share their medical and care records. In response to these targets the National Information Board (responsible for setting out strategies for data and technology in health and care) published a framework for action and strategic priorities for delivering the digital ambitions of the FYFV. Their report *Personalised Health and Care 2020* [112] initiated the development of digital roadmaps led by local Clinical Commissioning Groups (CCGs) to deliver the paperless vision.

In 2015 the National Advisory Group on Health Information Technology in England was established to advise the Department of Health and NHS England on its efforts to digitise the secondary care system. In 2016 this advisory group chaired by Professor Robert Wachter published its recommendations for the successful implementation of health information technology in England [113]. Among its ten recommendations the 'Wachter' Review stressed the importance of a continued drive towards digitisation, standards for interoperability to enable seamless delivery of care across organisational boundaries, as well as IT systems with user-centred design, and workforce development.

Key consideration: Digitisation of health data is the cornerstone of many personalised medicine applications. A continued drive towards the implementation of interoperable EHRs, with standardised data capture, is essential to realising the near-term and future benefits of personalised medicine.

Computing infrastructure

EHRs provide the essential digital foundations to capturing conventional patient data generated during clinical encounters. The development and delivery of personalised medicine will also require solutions for handling the vast amounts of data generated by high-throughput 'omics, and other data-intensive technologies (e.g. high-resolution imaging). Storage and analysis of these datasets consumes significant computer memory and processing power. Innovations in computational technologies and approaches, especially the growth of cloud computing, massive parallel computing, and data intensive computing tools offer promising solutions for handling large and complex datasets. These high-performance computational resources have been deployed for years by research institutions, but more recently there has been recognition that this underpinning digital infrastructure is needed in healthcare.

The 100,000 Genomes Project and plans for the National Genomics Medicine Service have paved the way in establishing informatics infrastructure for clinical whole genome sequencing. The growth in genomic datasets and the future integration of other 'omics analysis will continually stretch demands for computing resources.

Key consideration: In order to respond to rapidly evolving data needs for personalised medicine, it is essential the informatics and computing systems that are established are robust, interoperable and scalable to meet increasing demand.

One important development to support the use of scalable computing was the recent publication of national guidance on the use of cloud computing services for health and social care [114]. Cloud computing is storage and access of data and programmes over the internet, rather than on a local computer and its drive. The chief advantages of cloud computing is the ability to increase and add computational capacity on demand, in real time, without the overhead of managing the computing infrastructure which instead is overseen by the cloud provider.

Digital security, trust, and patient preference

Many of the information breaches historically reported by the health and social care sectors relate to patient information on paper [115]. Digitisation of health records presents a different set of security challenges to paper records. In particular cyber security vulnerabilities have the potential to endanger patient care and safety as well as undermine public trust in healthcare data sharing. Respective reviews by the Care Quality Commission [116] and the National Data Guardian (NDG) for Health and Care [115] have emphasised the importance of, and proposed recommendations for, strengthening data security and safeguarding patient data.

As with any sector, security provisions in healthcare must contend with the increasing sophistication of internet malware and cyber-attacks. Maintaining and upgrading data security is a constant requirement.

Key consideration: Secure safeguarded systems to protect data are central to fostering patient trust for the data sharing which is essential to conducting the high-quality research needed to drive personalised medicine.

In addition to data security, the NDG 2016 review [115] also put forward a proposal for a national data opt-out to give patients more control over how identifiable health and care information is used. These recommendations were accepted by the Government in 2017, and plans to operationalise the opt-out system are underway.

NHS Digital is creating a new system to support the national data opt-out that was introduced on 25 May 2018 alongside the new General Data Protection Regulation (GDPR). All health and care organisations will be required to uphold patient and public choices by 2020.

Key consideration: The development of novel personalised medicine applications will take place in the context of patient preferences for data sharing. Future planning for personalised medicine should consider the implications of the national data opt-out on the availability of health data for medical research and clinical services.

4.3 EHR dependent technologies

This section will describe some of the direct applications of EHRs for the personalisation of medicine using technologies that harness information contained with EHRs and/or integrate with the EHR system.

Clinical decision support

Clinical decision support (CDS) systems enable the provision of timely information to help inform decisions about an individual's care. For example, a CDS system may aid in identifying disease early, support accurate diagnosis or choice of pharmacotherapy. To generate clinically useful information, CDS typically combine a number of different information sources – e.g. biomedical knowledge, person-specific data, and including data imported from EHRs.

Clinical decision support systems encompass a broad range of tools – from databases relevant to particular patients, or alerts or reminders – that can be can be embedded into the EHR itself or function independently as standalone tools. CDS systems that enable risk assessment based on the combination of family and personal health history, are of particular relevance to personalised healthcare.

Risk assessment

Risk assessment is used in a number of different health contexts and settings to improve the provision of care. Assessment of risk is usually undertaken using tools based on risk prediction models. These models aim to predict risk based on a combination of known or measured characteristics and can be used to predict risk of current disease in those with symptoms, or to predict risk of future disease in asymptomatic individuals. The former is primarily used to guide further investigation whereas the latter is used to provide information on risk and to facilitate decisions on a specific intervention to be made.

These models and tools provide a risk score, which is a standardised metric for the probability that an individual will experience a particular outcome (e.g. develop diabetes or cardiovascular disease). Individuals may be stratified based on their risk score (e.g. into high or low risk groups) and different pathways of care offered within these groups.

The most well-known method of scoring risk for disease development is the Framingham Risk Score for cardiovascular disease. Methods have been developed for a number of other chronic diseases.

Current status of the field, implementation and use

Many risk prediction tools are already in clinical use in different clinical contexts for disease risk prediction (e.g. QRisk), or prognositication (e.g. NHS PREDICT). Attempts are being made to incorporate genomic information into new and existing tools in order to improve their discriminatory power thereby enabling better targeting of interventions.

Evidence in support of the incorporation of genetic information in the form of single nucleotide polymorphism data into disease risk prediction tools is available for breast cancer [117, 118] and cardiovascular disease [119] but is lacking for many other chronic diseases [120].

Many research studies have shown that incorporation of genetic information into risk prediction models may improve the stratification/discriminatory properties of the model, which could be useful in screening women [118]. However, evidence is lacking as to whether this has an impact on clinical care.

Family history tools

As a predictor of disease, knowledge of family medical history is in principle a relatively simple but powerful approach to personalised healthcare. It enables assessment of the risk of inherited conditions, single gene disorders and common diseases.

In practice there are a number of challenges to collation and effective utilisation of family history information.

How can family history inform personalised medicine?

Knowledge of family medical history can be used to:

- Identify if individuals are at increased risk of a certain disease (e.g. cancer, heart disease etc.) and offer a particular set of interventions based on this risk
- Establish patterns of transmission of genetic diseases
- Help guide decisions about genetic testing for an individual and family members
- Inform the interpretation of genetic test results

How is family history information captured?

There are a variety of methods available to obtain family history information and there is wide variation in the amount and granularity of information these approaches collect. Methods range from family history questionnaires through to checklists or pedigree tools. The most appropriate method/type of tool depends on the setting, patient population and intended use (e.g. risk assessment for prevention versus guiding diagnosis).

For example, comprehensive information along with detailed pedigree is required by genetic counsellors in assessing diseases with a strong genetic component.

By contrast this level of detail might not be required in primary care settings, where the needs are different. Tools are developed both by commercial organisations as well as academic institutions, and data may either be entered by the patient, clinician or in some cases both parties.

Current status of the field, implementation and use

There are a range of family history tools targeted for tertiary and primary care. The most advanced are usually designed for clinical genetics where there is a clearly defined role and requirement for family history details.

One of the few tools that have been validated in primary care to some degree is MeTree [121]. This is a patient facing software programme developed by the Duke Centre for Applied Genomics and Precision Medicine for collection of family history data in relation to a number of conditions. This information can be shared with clinicians and be used in clinical decision support, a component that has been developed for a number of specific diseases [122].

The implementation and evaluation of this tool has only been carried out in a limited number of clinical settings.

Some family history tools developed for use in clinical genetics are also interoperable with certain risk assessment tools, e.g. Phenotips, a pedigree drawing tool that is compatible with BOADICEA, a risk assessment tool for breast cancer.

Currently there a number of challenges to the routine, systematic collection of robust medical family health history and to the utilisation of this information:

- Typically data collection requires a concerted effort from health professionals as well as individuals and periodic updating is needed to ensure the data are accurate and up to date
- Clinical decision support in most cases in not a component of most available family history tools, resulting in uncertainly as to how physicians should act upon the information
- A number of tools have been developed by commercial companies and academic groups to overcome these challenges, but these have been validated to different degrees
- Evaluation of tools is challenging as there is a lack of reference standards against which to assess tools for their validity, reliability and benefit
- Systematic assessment of clinical utility, especially in the primary care setting, is lacking

Implementing and integrating risk assessment and family history tools

A number of tools are available for risk assessment and collection of family health history. They have been created either for multiple diseases or for specific disease.

The evidence base surrounding different tools is varied as is their uptake in clinical practice. The main gaps in assessing the utility of these tools is the lack of comprehensive assessment of where they add most value in care pathways, understanding the types of information needed in different care settings, and methods to assess which of the available tools are best suited in particular contexts.

There is also a lack of clear guidelines in relation to the use of these tools.

At a practical level the lack of interoperability of such tools with existing digital systems and EHRs also creates challenges for their uptake.

Key consideration: Whilst the value of risk assessment tools and family history data for personalised medicine is recognised – especially within genetics – their potential within secondary and primary care has yet to be unlocked. Beyond genetics, the development and incorporation of these tools can be supported by defining the contexts for when to use and clear mechanisms for how to use, including the types of information capture required and standards for interoperability with existing digital systems.

Summary

Clinical decision support systems incorporating risk assessment and family history data are an area of rapid development. The capabilities of these tools are likely to improve with advances in machine learning, analysis of electronic health records, and user friendly Apps and mobile interfaces. It will be important to understand the implications of the new EU *in vitro* diagnostics regulation on clinical decision support tools based on algorithms.

4.4 The age of personalised disease monitoring

In this section we briefly review a number of approaches that are enabling more frequent and/or detailed monitoring of health and disease. This group of technologies may help individuals and clinicians to:

- Respond more promptly to deterioration in health
- Better monitor and manage chronic conditions
- Detect symptoms or risk factors for disease earlier (before a condition manifests), and encourage preventative measures

More generally these tools are generating enormous volumes of data, which if integrated with other sources of health data (including the technologies reviewed in Chapter 3) can improve and enrich datasets for developing personalised medicine applications.

Each of the following categories is in essence a diagnostic or monitoring approach comprising an enormous range of different technologies and tools. Whilst there are a number of exemplars in each category that could, and are, being implemented, individually these are only likely to have an incremental impact on current healthcare. Significant impact on existing models of care, and implementation challenges of significant scale and complexity will arise as these approaches reach a tipping point in the number and extent of tools being adopted into the health system.

Notably more of these tools are being created and deployed for use outside of the health setting and as such are beginning to alter the dynamics of where, how, and by whom health-related data are generated.

Here we reflect on the key considerations this raises for the health system in the context of personalised medicine.

Point of care testing and portable diagnostic bioassays

Portable diagnostics bioassays (PDBs) are tools or devices that can diagnose (or monitor) disease including at or near the point of patient care or by individuals themselves. The portable, and increasingly compact 'hand-held' nature of these devices and their self-contained testing mechanism makes them amenable to personal-testing or monitoring and point of care testing (POCT).

The advantage of portable devices are:

- They eliminate the need to move biological samples to a laboratory setting for testing and analysis
- They can enable tests to be carried out by non-laboratory healthcare personnel
- They can enable individuals as opposed to healthcare professionals to diagnose (or monitor) disease

Point of care testing applications are a major focus for developers of portable diagnostic bioassays. POCT is usually defined as medical testing at or near the site of patient care, outside of a conventional laboratory, carried out by health professionals [123]. These typically include health professionals in a hospital, clinical or ambulatory care setting or at home, or in a community setting by a patient. The aim of POCT is to facilitate faster decision-making about a patient's care and management, by obtaining accurate results in a very short time period.

Point of care testing devices have differing levels of complexity, ranging from dipsticks (e.g. glucose testing) to complex molecular or imaging systems (e.g. portable ultrasounds). Innovations in technologies such as DNA sequencing, microfluidics, and microelectronics are driving the growth of portable devices that can perform complex assays that were traditionally the domain of laboratories.

Current status of the field, implementation and use

A number of different technologies form the basis of POCT and PDBs and they are a major area of innovation within the diagnostics industry [124]. Drivers of the development of POCT and PDBs include demand for technologies that can be used in low resource settings, the rising incidence of common chronic diseases (e.g. diabetes, cardiac disease), increasing home-based PDB usage and the move towards more patient-centred care.

Despite the growth in number of POCT devices and PDBs their rate of implementation in clinical practice is varied and dependent on the:

- Exact application and if this is related to an unmet health need
- Impact on the care pathway
- Analytical performance compared existing established laboratory tests (where these exist)

Portable ultrasounds are one example of a device that has been implemented more rapidly, as the technology already has a history of clinical utility in particular settings, and the devices do not significantly alter current care pathways because they are in essence a miniature version of the pre-existing ultrasound technology. However, the utility of many other types of devices is dependent on adjustments to care pathways to incorporate near-patient testing and to respond to more rapid results.

Implementing and integrating PDBs and POCT

PDBs and POCT are burgeoning areas of development with further progress likely to be driven by improvements in underpinning technologies (e.g. microfluidics, sequencing).

Expansion in the adoption of these devices will accentuate existing challenges to implementation:

- Demonstrating sufficient accuracy, validity and value in particular clinical contexts
- Ensuring oversight of devices/kits, quality of and consistency of results across different devices
- Assessing potential impact on the care pathway
- Identifying which PDBs are suitable for POCT
- Training of end users
- The capture and management of results into EHR

Key consideration: The effective utilisation of POCT devices could be supported by an assessment of the clinical contexts within which POCT is likely to have the greatest impact on patient outcomes and an assessment of how care pathways may need to adapt to maximise the utility of these devices.

mHealth and digitally enabled wearables

mHealth, an abbreviation for mobile health, is a term to describe health related applications delivered via a mobile device such as a phone, tablet or digital watch. An mHealth app is a computer program that runs on the mobile device that allows the user to monitor and manage disease/health or provides health related education or encouragement for behaviour-change.

mHealth apps can collect data about the user through:

- Sensors on the mobile device: e.g. camera, accelerometer, gyroscope
- Direct user input/engagement
- Synced devices: e.g. blood glucose monitor; or digitally enabled wearables and sensors e.g. smart watch

Digitally enabled wearable devices can be integrated into wrist bands, wrist watches, shoes, eyeglasses and other garments to allow continuous physiological monitoring with little manual intervention. Sensors in these devices may monitor heart rate, physical activity, skin moisture, and blood pressure. Examples of emerging wearable technologies include augmented reality glasses, and smart contact lenses that check blood glucose levels.

Increasingly the line between lifestyle and medical devices is beginning to blur; last year the FDA cleared a device accessory for the Apple smart watch that takes electrocardiogram readings. A major advantage of medical mHealth and wearables is the ability to collect health-related data outside of a healthcare setting.

With the growth in mHealth activity, NHS England have launched a public-facing Digital Apps Library to host healthcare apps that have either been approved or are being tested in the NHS, and a Mobile Health space for app developers to submit their apps for assessment for inclusion in the App Library. Some apps are being developed for use directly by healthcare professionals. One example being the DeepMind Streams app, which syncs patients' electronic healthcare records and their vital recordings to predict and alert clinicians to patients experiencing acute kidney failure.

However, the vast majority of available and emerging mHealth and wearables technology are direct to consumer. Depending on consent polices the user generated data can be shared with the hardware or app developers, who may use the information to improve the performance of their product, or for health research activities.

Key consideration: The health system will need to assess whether and how to engage with the growing consumer-driven digital health movement.

Implantable sensors

Implantable sensors are biosensor devices that can be implanted under the skin or elsewhere in the body to monitor blood analytes. Similar to mHealth and wearable technologies, these devices could enable remote data acquisition – outside of the healthcare setting – and on a continuous basis.

At present implantable biosensor technology is still maturing, although in principle the potential future applications for these devices are only limited by the physiological measurements they can assess. Advances in nanomaterial and wireless technology are driving improvements in biosensor miniaturisation and signalling to transmit data.

The most promising application to date is for diabetes management whereby a continuous glucose monitoring sensor is inserted under the skin, the readings are sent to a device which calculates the correct insulin dose and communicates this to a body-worn insulin pump that automatically administers the correct dose. As well as chronic disease management, implantable biosensors could in the future impact drug development and treatment monitoring, post-operative care, and early disease detection.

Summary

Personalised disease monitoring is a rapidly expanding area, driven by developments in portable, wearable, and implantable biomedical and digital technologies. These broad range of tools and devices are at different stages of development and deployment and many are designed for use outside of the health setting. As the number and capabilities of these devices increases it will be important to consider how these tools and the data they generate can be most effectively harnessed.

4.5 The internet of things for healthcare

The Internet of Things (IOT) is an interconnected communication system involving a number of digital devices or SmartThings. It can be thought of as networking between two or more physical devices that contain electronics, software, sensors and network connectivity allowing them to collect and exchange data with each other.

Indeed, many portable diagnostics, mHealth, wearables and sensor devices described in this chapter operate on this basis; they connect and network with at least one other device – usually a mobile or computer, that will usually store, analyse and/or display the data being collected.

IOT networking can also be extended to the web and cloud-platforms, where data captured from devices can be stored and analysed.

IOT applications for healthcare are often referred to as the Internet of Medical Things (IOMT). The benefit of IOMT is easier access to and quicker flow of information that will enable improvements and greater efficiencies in the provision of care.

Devices and IOMT-based services being developed and projects supported by NHS Testbeds, include:

- Connected inhalers that record and have the ability to transmit usage data to a digital platform, allowing patients and clinicians to examine usage and adherence
- CoaguCheck INRange which enables international normalised ratio self-testing (to inform anticoagulation therapy) and transmit results directly to the healthcare provider
- Technology integrated health management for dementia: a two-year NHS Test Bed project which is aiming to identify technologies that can be placed in people's homes to improve care for people with dementia
- Diabetes Digital Coach is examining the use of remote monitoring and coaching technology for better self-management.

The IOMT market is projected to grow significantly in the next few years, and estimates suggest by 2020, 40% of IOT technology will be health related [125]. There is also a growing range of non-medical IOT devices, from smart home sensors to environmental monitors that may generate health-relevant information.

Currently many IOT devices operate within closed proprietary platforms that are often not cross compatible with other manufacturers' systems/devices.

If greater interoperability between different systems and devices is achieved, then IOMT could help to address the substantial challenge of integrating different datasets generated across a range of disparate medical devices. Doing so is not without significant challenges to overcome in data security and standards for interoperability. Moreover, actionable insights from these integrated datasets will rely on the development of real-time informative data analytics.

As communication systems, data transfer protocols, and machine learning techniques continue to improve, IOMT and more generally the IOT could have a substantial impact on healthcare.

Summary

IOT platforms are one approach to addressing the challenge of transferring and integrating the increasing volumes of data arising from the portable, wearable, and sensor devices described in this chapter. As communication systems, data transfer protocols, and machine learning techniques continue to improve, IOMT and more generally the IOT could have a substantial impact on healthcare.

4.6 Remaining agile in a fast-developing digital world

We are witnessing the emergence of a range of miniaturised and portable medical and non-medical devices that can be connected to one another and to data capture and analysis systems via the internet. In principle, these devices could radically transform the landscape of when, where and how healthcare activities take place. Moreover, the widespread diffusion of mobile technology, mHealth and wearables will provide a rich source of health-related data to catalyse the development of personalised health approaches by commercial and research entities.

Looking forward it is likely, therefore, that a significant contribution to both diagnostic and therapeutic personalisation will be made by digital tools and devices over which the health system has little or no control. Consequently, the health system will need to adapt from being the primary generator of patient health data to being part of an ecosystem in which it does not control or generate a significant proportion of the data and information that may be relevant to a patient's care or maintenance of health and wellbeing.

Whilst there is growing interest in integrating data from sensor technologies and mHealth apps within EHRs, there is not yet an overarching strategy for harnessing the expanding consumer driven aspects of the digital health revolution. If the health system wishes to engage in this, it will be important to ensure that the digital infrastructure being established towards paperless records and for personalised healthcare can accommodate the rapid developments in consumer-facing digital health tools. For example, long-term arrangements with inflexible closed enterprise software and hardware solutions could significantly restrict the ability to integrate or incorporate the benefits of citizen generated data and the IOT.

Key consideration: The health system should seek to develop policy on whether and how to fully harness the benefits of consumer driven, citizen generated, health data

Key consideration: The underpinning informatics hardware and software solutions being established across the health system should be sufficiently agile and flexible to respond to the rapidly evolving capabilities of digital health technologies

4.7 Data analytics and the role of artificial intelligence

The advancement of personalised medicine relies on the ability to mine, analyse, and derive new insight from the enormous volumes of data generated by the digital technologies described in this chapter and the 'omics approaches of the previous chapter. In combination with high-performance computing, artificial intelligence is arguably having the most profound implication on 'big data' analytics witnessed in recent times owing to its potential to extract knowledge from large quantities of data in ways that was not previously possible.

Significantly, the technology can uncover patterns in large and complex datasets that would not easily be apparent or perceivable to humans, helping to lead to new insights and greater stratification of patients for disease prediction and prognosis.

What is artificial intelligence and machine learning?

Artificial intelligence (AI) is an umbrella term used to describe the design of computing systems that make machines work in an intelligent way (Box 4.1). Machine learning (ML) is a type of AI that provides computers with the ability to learn without explicitly being programmed. In contrast to conventional, rules-based programming – where computers are instructed by 'man-made' algorithms to complete a task, ML algorithms iteratively learn from large datasets to discover their own rules and can therefore improve with experience. Crucially machine learning technologies rely on existing datasets to train the algorithms. The main objective of ML algorithms is to perform classification, prediction, estimation or similar tasks.

What's the significance of artificial intelligence and machine learning in healthcare?

Artificial intelligence and machine learning technologies present a fundamental shift in data analytics capability with profound implications across a number of domains of healthcare delivery and for personalised medicine research and development.

Broadly, the applications of machine learning in health and research relate to:

- The automation/semi-automation of tasks currently performed by humans, e.g. segmentation of medical images for precision radiotherapy planning
- Mining of large datasets to uncover novel patterns and insights for discovery, e.g. novel disease biomarkers or drug targets
- Prediction of health and disease by complex pattern recognition, e.g. disease detection and diagnostics; clinical decision support

Box 4.1 Definitions

- **Artificial intelligence** is the development and use of computing systems concerned with making machines work in an intelligent way
- **Machine learning** is a form of artificial intelligence that uses algorithms which iteratively learn from data rather than being 'explicitly programmed'. Performance tends to improve with experience and more datasets
- **Training data** are the datasets used to develop and improve the performance of machine learning algorithms
- **Computer aided diagnostics or detection** are algorithms that assist with the interpretation of medical data and images. These can be based on conventional programming or ML algorithms

A huge amount of research is underway to explore the potential of machine learning for health delivery and for basic science. The vast majority of artificial intelligence health research is within the discovery or proof-of-principle phase; this is demonstrating the applicability of machine learning approaches for:

- Providing enhanced diagnostic capability (e.g. schizophrenia [126] and Alzheimer's disease [127])
- Enabling treatment stratification (e.g. breast [128] and lung [129] cancer)
- Disease prognosis predictions (e.g. breast [130] and lung [131] cancer)
- Generalised longevity predictions (e.g. using CT medical images [132])

Within the UK some artificial intelligence solutions are being developed or trialled in collaboration with commercial groups and the health system (Table 4.1). Larger and multi-centre studies will be key to progressing these examples further towards clinical translation.

Table 4.1: Examples of UK based AI developments or trials

Condition/field	Organisation(s)	Description – objective
Cardiology	Ultromics – trials taken place across six NHS cardiology centres	An AI based echocardiography software for the diagnosis of coronary heart disease [133].
Radiology	Microsoft Research - InnerEye Project	ML techniques for the automated segmentation of 3D radiological images for radiotherapy planning or surgical planning [134].
Ophthalmology	Moorfields Eye Hospital and DeepMind	Algorithms for analysing retinal scans to identify eye diseases [135].
Oncology	University College London (UCL) Hospitals NHS and DeepMind Cancer Research UK (CRUK) and DeepMind	UCL Hospitals – DeepMind: ML approach to plan radiotherapy for head and neck cancers [136]. CRUK and DeepMind: ML to improve breast cancer diagnosis [137].
Patient triaging	North Central London CCG and Babylon Health	Mobile app triaging system in place of NHS 111 [138].
Patient queries	Alder Hey Children's Hospital and IBM Watson	An AI powered chatbot that allows children and their parents to ask questions about their hospital experience [139].

Machine learning and advanced image analysis

The most immediate impact of artificial intelligence and machine learning in health is likely to be realised within medical image analysis. Studies indicate artificial intelligence algorithms trained on images of skin lesions could perform on par with dermatologists in the classification of different types of melanoma and prediction of malignancy [140].

Machine learning approaches are being developed for automated image segmentation of brain tumours [141] and multiple sclerosis plaques [142].

An artificial intelligence based imaging technology (HeartFlow FFRct) which creates a personalised, 3D model of a patient's arteries to assess blood flow and the impact of blockages was recommended by NICE in 2017 [143]. Another AI assisted cardiac imaging system (Arterys Systems) was FDA cleared in the same year.

Artificial intelligence within radiology for the interpretation of X-rays, MRI, and CT images is gaining significant traction [144]. The potential within pathology imaging is also recognised, but in contrast to radiology where images are predominantly now captured and stored digitally, progress in pathology is hindered by the lack of digitisation.

In recognition of the enormous potential in these areas one ambition of the Life Sciences Industrial Strategy is the development of artificial intelligence technologies to transform radiology and pathology.

As the strategy notes, the digitisation of pathology workflows is an essential first step to realising the benefits of machine learning in this field. More immediately digitisation would afford substantial efficiencies in NHS pathology services through greater virtual working and 'reducing the need for every hospital to have the full on-site set of pathologists'[145].

Realising the potential of artificial intelligence within the health system

The NHS is recognised as an incredibly valuable resource for advancing artificial intelligence but for reasons noted earlier in this chapter it is not yet equipped to capitalise on the data it collects. Factors include:

- Lack of digitisation of health data and patient records
- Differences in data labelling and acquisition between departments and Trusts
- Challenges to sharing data across departmental and organisational boundaries
- Public perception and trust

Going forward if the health system wishes to harness the transformative potential of artificial intelligence, essential considerations include:

- The value of a national approach to creating training datasets for algorithm development
- Standards for data formatting, exchange and interoperability
- Strategy for supporting the curation and preparation of data for training AI approaches
- How to access AI and machine learning expertise
- How to integrate AI approaches appropriately and effectively
- Public engagement and dialogue on the use of these technologies in healthcare

Summary

Artificial intelligence is a rapidly evolving field with enormous potential to drive progress across the range of technologies reviewed in this report and the personalisation of medicine more generally. Machine learning approaches are a significant turning-point for the analysis of large datasets and could help expedite novel discoveries for personalised healthcare. Currently medical image analysis is among the most promising applications of artificial intelligence technologies. Radiology and histopathology, in particular, have been highlighted as areas that could be transformed by AI. Since digitisation is a fundamental pre-requisite to realising the benefits of this technology, in Chapter 5 we will review how the broader adoption of digital pathology could be achieved, and we briefly discuss the challenges to applying AI in advanced image analysis in radiology and histopathology.

Personalised medicine in the NHS - delivering on the promise

In this chapter we review specific shortlisted technologies from the earlier chapters in more detail and assess how they could be integrated into the health system in a way that realises benefits for the whole patient population. We also describe technologies that are pertinent to areas of strategic interest for the NHS.

Whilst some of these technologies are not expected to present major service requirements in the next one to three years based on our methodology (Section1.5), they have been identified as key strategic areas and we therefore explore how they could be integrated in the future and how the health system can prepare for the maturation of these technologies.

5.1 Introduction

A number of the technologies described in Chapter 3 are potentially ready for implementation now or could be within the next three years and their implementation could deliver near-term or immediate benefits for personalising patient care. These technologies were shortlisted on the basis of our methodology (Chapter 1) and if they met a number of these specific criteria:

- A strong research base demonstrated by extensive research publications
- Are implemented in the health system on a small scale or are being considered for implementation by the health system (e.g. by NICE)
- Has evidence of clinical validity and utility from large-scale late stage clinical trials, or clinical trials are underway that are due to report in 2018–19.
- Have been implemented in other comparable health systems

The technologies

The technologies and their applications that according to our analysis meet the criteria of being implementation-ready are:

- ctDNA: circulating tumour DNA testing for treatment selection in oncology
- Transcriptomics: gene expression panel tests for cancer prognosis and treatment decisions
- Pathogen genomics: tuberculosis whole genome sequencing, WGS for outbreak management in hospitals
- 3D imaging and printing: surgical guides, anatomical models, custom implants

Other areas of strategic importance that were reviewed are:

- Pharmacogenomics: genotype guided drug dosing, testing to avoid adverse drug reactions, and medicine optimisation
- Advanced image analysis: including digital pathology, machine learning, AI
- Regenerative medicine: gene therapy and stem cells

5.2 Circulating tumour DNA testing

Circulating tumour (ct) DNA testing – analysis of genetic material from a blood sample, or liquid biopsy, is a technology that has demonstrated clinical utility as a companion diagnostic test and also has great potential as a monitoring tool, for example to determine emergence of resistance to therapy or to detect relapse after treatment [146].

Testing of ctDNA is currently used on a small-scale within the NHS as a companion diagnostic test in non-small cell lung cancer (NSCLC). This involves measuring *EGFR* mutation status to determine if a targeted therapy can be prescribed. The laboratories offering testing are also exploring the use of companion diagnostic tests in other cancers (*BRAF* in melanoma [147] and *KRAS* in colorectal cancer [148]), and there is an extensive amount of research and clinical trials ongoing to explore the use of ctDNA testing to stratify patients for treatment [51] and to monitor treatment success [52].

This is a fast-moving area of research and clinical development so the health system will need to prepare for the growing use of ctDNA liquid biopsy for treatment selection beyond NSCLC, and also for future uses such as patient monitoring once the evidence and technologies mature.

In this section we will review developments in the use of liquid biopsy in NSCLC as this area is the most advanced in terms of clinical availability and consider how the experience gained and lessons learned in establishing this test could help to inform the broader integration of ctDNA liquid biopsies into the health system.

Evidence for implementation of ctDNA testing for therapy selection

Current use in the NHS

As of October 2017, ctDNA testing for NSCLC had been implemented in seven UK NHS laboratories, with services planned or in development in a further five laboratories. The first services were implemented late in 2015.

Companion diagnostic testing in NSCLC involves carrying out a genetic test on a sample of solid tumour tissue obtained during a tumour biopsy, to determine if the tumour harbours one of a defined set of mutations in the *EGFR* gene. Presence of any of these mutations means that a patient can be prescribed targeted tyrosine kinase inhibitor (TKI) therapy. However, in 30% of cases solid biopsies fail and a genetic test cannot be carried out – ctDNA testing in these cases is a viable alternative [48, 149].

Several factors contributed to the development of ctDNA testing services for NSCLC in the UK:

- The expectation of licencing allowing ctDNA testing as a companion diagnostic to osimertinib (3rd generation TKI).
- Availability of a CE-IVD marked kit, Roche cobas®, for testing, and other technological advances in the sensitivity and usability of ctDNA technologies
- ctDNA testing complements current solid tumour testing for *EGFR* performed in laboratories
- The availability of stabilising tubes improving the logistics around sending blood samples to laboratories
- Clinical unmet need – patients not accessing genetic testing, and targeted therapy, due to solid biopsy failure
- Laboratories willing to develop testing, supported by clinicians and pharmaceutical companies

ctDNA testing is currently used in two situations in NHS clinical practice for lung cancer management:

1. At diagnosis in cases of biopsy failure (specifically when there is not enough biopsy material for a genetic test), to determine if a patient's tumour has mutations in *EGFR*. If a mutation is present 1st or 2nd generation TKIs can be prescribed – afatinib, erlotinib or gefitinib
2. As a first-line test when tumours in patients on 1st/2nd generation TKIs progress, to determine if resistance to therapy is caused by an additional mutation in *EGFR* called p.T790M, for which a 3rd generation TKI, osimertinib, is available. A solid biopsy can be tried if the test fails or is negative.

ctDNA testing can have an impact on NSCLC patient outcomes by:

- Increasing accessibility of genetic testing to patients who have a failed biopsy – all eligible patients should have their *EGFR* mutation status assessed
- Improving testing access and optimising prescribing of targeted therapy that has been approved as being cost-effective for patient use. TKIs benefit patients by having fewer side effects and also longer progression-free survival compared to standard of care chemotherapy
- Reducing the number of patients with advanced cancer who will have to go through another solid tumour biopsy – a more expensive and invasive procedure with potential side-effects – to determine if the p.T790M mutation is present

Solid tumour *EGFR* mutation testing is recommended as part of the NSCLC patient pathway to determine *EGFR* mutation status after solid tumour biopsy [150]. Given that solid tumour testing should already be standard practice, ctDNA testing can complement solid tumour testing as outlined in the points above. The cost impact of using this technology is not clear, however. While a ctDNA test is cheaper than a solid tumour biopsy [151], it is not known how this affects the overall cost of treating the patient. Health economic analyses are urgently needed to answer this question.

Despite the availability of ctDNA testing, it is not yet in widespread use and not all eligible patients receive testing. There is an opportunity to learn from current laboratory experience about how implementation can be supported now and in the future since the foundations have already been laid to integrate ctDNA testing into the patient care pathway for NSCLC.

The health system can build on the expertise that has already been developed by laboratories and clinicians delivering testing and should consider how this might be integrated into the planned national genomics laboratory structure. There is also a need to integrate new service information as it becomes available, such as the results of ongoing external quality assurance and service evaluation studies.

Possible further uses of ctDNA testing include monitoring emergence of resistance to therapy – for example NSCLC patients could be tested more regularly for p.T790M – or after treatment to detect ctDNA as a marker for relapse, for example after chemotherapy or surgery [152, 153]. The advantage of using testing in this way is that clinicians can adjust treatment more quickly, for example before radiological progression. Currently more research is needed to develop these approaches and establish what the impact on clinical outcomes and benefits will be.

Barriers to the use of ctDNA testing – how can test implementation be supported?

The challenge is to ensure that ctDNA testing is available to all eligible patients equally and equitably. There are a number of issues that will have an impact on the use of ctDNA testing, which once addressed will support the implementation of the technology into the NHS. Some of these challenges have already been explored in the context of NSCLC [50, 154] and highlight issues that are pertinent to the broader implementation of this technology.

Guidelines

The only guidelines currently available in the UK that recommend *EGFR* ctDNA testing are those issued by the Scottish Medicines Consortium advice on osimertinib, which recommends use of a plasma test to detect p.T790M with a tissue test as second-line test if needed [155]. NICE guidelines on companion diagnostic testing for *EGFR* only cover solid tumour testing. However a recent Medtech Innovation briefing (MIB) outlined uses for plasma *EGFR* testing but also highlighted uncertainty surrounding rapidly evolving technologies and what constitutes the gold standard test [151]. This MIB is an important first step in formally outlining the benefits of ctDNA testing, but also some of the remaining challenges.

International guidelines from Australia recommend that a plasma test can be used to detect *EGFR* p.T790M [156] and recent guidelines from the National Comprehensive Cancer Network in the United States state that plasma testing should be considered if there is not enough solid biopsy material for genetic test [157]. Guidelines from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology (US) also recommend the use of ctDNA testing to confirm *EGFR* mutation status when not enough tissue is available [158]. No guidelines recommend the use of ctDNA testing for diagnosis of NSCLC.

The lack of clinical guidelines on how and when to use testing creates uncertainty among users. Clinical data needs to be collected on when during clinical progression is best to test and also to answer questions such as: can testing be used for monitoring? What are the implications for patients in changing treatment if ctDNA indicates progression but this cannot be seen radiologically?

Key consideration: To support NHS implementation clinical guidelines on the use of ctDNA testing in NSCLC should be considered. These could be developed by one or more of the professional societies and organisations, such as: British Thoracic Oncology Group, British Thoracic Society, Royal College of Pathologists, Cancer Research UK (including the Experimental Cancer Medicine Centres network), NICE (clinical guidelines for lung cancer). Clinician and laboratory expertise in ctDNA testing should be actively collected to inform these guidelines.

Technology development – what is the best test?

In terms of technology development, there are high-levels of interest in this area, especially in the United States, with many companies developing technologies and/or panel tests to detect mutations in a range of solid tumours – particularly lung, breast, prostate, colorectal, melanoma. There are three CE-marked tests available for ctDNA-based *EGFR* tests: Qiagen Therascreen, Roche cobas® and AmoyDx. The only FDA-approved liquid biopsy is Roche cobas®. Laboratory-developed tests are also available in the United States via clinical laboratory improvement amendments-certified laboratories. UK laboratories currently have a mixed approach to test development, with some developing in-house digital droplet PCR tests and others validating commercial tests.

There are a number of initiatives underway to assess ctDNA testing and services. External quality assurance investigations for *EGFR* tests are taking place internationally, coordinated by the International Quality Network for Pathology. NHS service evaluation is currently ongoing by a number of laboratories. The health system should be ready to respond when the results of these efforts are known and consider what the implications are in terms of future test development, for example is it more effective to implement commercially available tests, in-house developed tests, or a mixed model?

Key consideration: Ongoing service evaluation is required to ensure that the health system has the appropriate information for informing further implementation.

Table 5.1: Examples of available liquid biopsy tests/platforms:

Test	What it measures
Roche cobas®	Panel of *EGFR* mutations, NSCLC CE-marked and FDA approved
Qiagen Therascreen	Panel of *EGFR* mutations, NSCLC CE-marked
Inivata	Panel of 36 genes for NSCLC. In partnership with Genomics England.
Natera	Personalised ctDNA panel based on mutations found in a patient's solid tumour. Used in the CRUK TRACERx study to monitor recurrence after surgery.
Guardant Health	Guardant 360 panel containing 73 cancer mutations. Looks for clinically actionable mutations and those with clinical trial potential.
Trovagene	Liquid biopsy for *EGFR*, *KRAS*, *BRAF* (urine or blood)
Foundation Medicine	FoundationACT – ctDNA for 62 genes. Findings linked to targeted therapies and clinical trials.
Amoy Dx	Two kits that detect 41 mutations in *EGFR* (SuperARMS *EGFR* mutation detection kit) and T790M (SuperARMS *EGFR* T790M mutation detection kit) CE-marked
Panagene	PANAMutyper R *EGFR*. Detects 47 mutations CE-marked, but for solid tumour testing only
Bio-rad	Droplet digital PCR Dx system (13 mutations) CE-marked

Engagement within the health system

Knowledge about, and engagement with, ctDNA testing varies between different individuals and parts of the health system. This results in regional differences in availability of testing and in which patients receive testing. The issues encountered are: lack of engagement within the health system about what ctDNA testing is, what it can be used for, its limitations and also how to access testing. This challenge is not unique to *EGFR* testing in NSCLC and engagement about all forms of ctDNA testing should be considered in the broader context of informing the health system about the benefits of genomics.

Key consideration: Engagement about ctDNA testing can take place within the multidisciplinary team – ideally via an individual who can act as a point of contact for queries and information. This person could be a clinician, clinical scientist or a pathologist.

Service logistics

Circulating tumour DNA starts degrading once a blood sample has been collected and white blood cells within the sample release further wild-type DNA following apoptosis or cell lysis. As such, blood samples for ctDNA testing should be collected in tubes that contain a preservative to stabilise the sample. In order to ensure that oncologists have access to these tubes, laboratories send them to the clinical team when a test is requested. This process requires effective communication between laboratory and oncologist, and also that the relevant logistical information is easily accessible.

Key consideration: The use of laboratory websites to include up-to-date and clear electronic referral information and resources, including testing information, costs and logistics should be considered.

Health system challenges and initiatives

Current ctDNA testing services in NSCLC were developed in response to a number of factors by a small number of centres in a relatively short time-frame (one to three years). As such, there is currently a lack of formal consideration by commissioners for the provision of ctDNA testing services in lung cancer, which is contributing to regional variations in service provision. In addition, there is a lack of clarity among test users over test funding, not just payment for tests but also what resources are available for test development.

There is also a challenge to be met in terms of the approval process for targeted therapies – currently the companion diagnostic tests needed to prescribe these therapies appropriately are not approved in parallel.

However, the procurement of national genomics laboratory services will have a significant impact on the delivery of genetic testing in England (Chapter 2). Each Genomics Laboratory Hub (GLH) will concentrate expertise into centres of excellence and there is an opportunity to capture and make the most of the expertise already gathered in terms of developing and delivering ctDNA testing in NSCLC. Measures are already being put in place to ensure that GLHs have the capacity to handle plasma samples such that the nucleic acids they contain are preserved for downstream testing.

Supporting and strengthening current testing in NSCLC will provide a solid foundation to ensure that potential future uses of testing can be realised by the GLHs as technologies mature. These include extending companion diagnostic testing to other cancers and drugs, monitoring relapse or emergence of resistance due to drug treatment, and monitoring relapse after surgery.

Key consideration: Healthcare commissioners should formally consider the provision of ctDNA services in lung cancer, including whether *EGFR* ctDNA tests should be included on the National Genomic Test Directory, and improve and strengthen current service provision.

Key consideration: Future service development efforts should consider how the results from current service evaluations and external quality assessment, key lessons learned and expertise in ctDNA testing in NSCLC could be captured and incorporated to inform future uses and delivery of other ctDNA tests by the health system.

Key consideration: The health system should assess how the establishment of ctDNA testing services and their validation could be supported by the promotion of available funding, promotion of test funding structures, linking of test development into accelerated access of technologies and support of collaborative test development.

Key consideration: NHS England should consider how patients can have improved access to funded targeted therapies and take steps through policy development to ensure that the health system is better prepared to implement targeted therapies when commissioned.

5.3 Pathogen whole genome sequencing

This analysis focuses on the two areas where pathogen whole genome sequencing (WGS) is either being used or has potential uses in the management of infectious diseases:

- Tuberculosis identification, antimicrobial susceptibility and outbreak detection
- Outbreak detection and management in hospitals

Why pathogen genomics?

Sequencing the whole genome of pathogens has some advantages over conventional genotypic and phenotypic methods:

- For some pathogens, WGS is quicker and cheaper
- The information from WGS is the highest possible resolution and also provides multiple pieces of information about a pathogen. In effect, WGS can replace multiple phenotypic and genotypic tests
- Genetic sequences can be used to inform outbreak epidemiology by comparing the genome sequence of organisms to single nucleotide resolution in order to determine relatedness
- Stored sequence information contributes to the extensive back-catalogue of genomes which can be used to inform outbreak detection and to monitor the spread of antimicrobial resistance (AMR)

Tuberculosis whole genome sequencing service

The tuberculosis WGS service is run by Public Health England (PHE) since *Mycobacterium tuberculosis* is a notifiable organism of public health importance.

The WGS service for TB was established due to some of the challenges associated with diagnosing the disease and also of determining the susceptibility profile of the organism in a timely manner. This process could take over six weeks and is particularly problematic for multi-drug resistant and extensively drug resistant TB, where treatment often starts before full diagnosis and the susceptibility profile is known.

The PHE National Mycobacterial Reference Service (NMRS) in Birmingham is carrying out WGS on all TB specimens from the Midlands and north of England, this included sequencing an extensive back catalogue. The London NMRS started WGS for TB specimens for London and the south of England in October/November 2017, extending coverage to the whole of England [159].

Tuberculosis is currently the only pathogen for which WGS is used for diagnosis, antimicrobial susceptibility profiling and outbreak management.

Table 5.2: WGS vs. conventional methods for tuberculosis

What	Pre-WGS	WGS	Reference
Whole pathway time (median)	31 days	9 days	[160]
Identification time (median)	1 day	6 days	[161]
Susceptibility testing time (median)	12 days	8 days	[161]
Cost (per specimen, analysis to final report)	£518	£481	[160]

Although identification is slower with WGS, the generation of the final report is quicker ensuring that patients receive accurate treatment sooner. A recent paper assessing the WGS pipeline side-by-side with conventional pathways showed that WGS predicts species and drug susceptibility with great accuracy however work is still needed to improve these predictions and also to reduce laboratory processing time [162]. The cost of the WGS pathway is expected to fall over time given the continuing decrease in the costs of sequencing.

Impact of tuberculosis whole genome sequencing service on the NHS

In terms of how WGS implementation affects the NHS, the pathways in terms of sample delivery remain the same for clinicians. The difference is in the information returned and how it is returned – currently in the form of a report that includes identification and the antibiotic susceptibility profile of the infection. All of the WGS data are stored by PHE.

Guidelines for tuberculosis management are available via NICE, including in NICE Guideline 33 [163]. WGS is not yet included in the guidelines for diagnosis of active TB. This could have an impact on the awareness of WGS technology more broadly within the health service.

Another area which could have an impact on the management of TB within the NHS is culture-free sequencing. The time taken to grow bacterial culture for sequencing is still a barrier to reducing turn-around times and to providing rapid WGS diagnostics. While PCR-based tests are available that can give a rapid result directly from a sputum sample for certain antibiotic resistance genes, e.g. the GeneXpert MTB-Rif assay, further phenotypic tests are needed to confirm diagnosis and to fully determine the antibiotic resistance profile of the pathogen.

Research exploring the use of culture-free sequencing is ongoing. Early results show that Illumina-based WGS can deliver results on identification, more common antimicrobial susceptibility information and epidemiological information within 48hrs. Portable long-read MinION sequencers can deliver results in less than 12hrs, with costs ranging from £96 to £515 per sample depending on the sequencing modality used [164]. A case study on a patient with drug-resistant TB showed that WGS directly from sputum samples gave the clinical team valuable information about the resistance profile of the infection in a short-time frame, allowing them to alter the treatment regimen and minimise toxicity to the patient [165].

While culture-free sequencing is more challenging, particularly in distinguishing TB from human and other bacterial DNA, it could provide a more accurate profile of a patient's infection. It is possible that some TB bacteria in a sample grow better than others, as such, certain isolates might be over-represented in culture and not necessarily reflect the full spectrum of the infection.

Considerations for NHS England

Many of the questions surrounding the cost-effectiveness of the service and clinical utility fall within the remit of PHE as the WGS provider. In terms of service use, NHS testing services still undergoes the same procedures in terms of submitting samples to PHE. Given advances in sequencing technology, NHS England could consider:

- Data sharing needs between NHS services and PHE – what are they and do measures need to be put in place to facilitate data transfer between the organisations?
- Are the clinical needs of the NHS being met by the WGS service? Feedback of information from the NHS to PHE required about how the service is operating and what changes might need to be put in place.
- Preparation for culture-free sequencing: collaboration between PHE and NHS services to determine whether portable and/or culture free sequencing will alter where sequencing is carried out and by whom, and the impact this could have on sequencing service delivery

Whole genome sequencing for outbreak management in hospitals

The management of large-scale outbreaks of pathogens of public health importance, including notifiable pathogens and diseases, is the responsibility of PHE [166], who carry out the necessary surveillance activities and also put measures in place to bring outbreaks to a conclusion. PHE now use WGS as the routine analysis tool for at least seven pathogens [167]. Policy documents, including from the European Centre for Disease Prevention and Control, recommend using WGS for outbreak management, particularly foodborne diseases [74].

There is, however, a role for WGS in the management of outbreaks both in hospitals and public health settings that fall outside the remit of PHE. While many infection control practices are highly effective in controlling infections when implemented correctly, situations do arise when outbreaks are not brought under control. Conventional methods of outbreak investigation can lack the resolution necessary to determine the source and transmission of such outbreaks.

One study used WGS to investigate an outbreak of *Pseudomonas aeruginosa* in a hospital burns unit. The source of the infection was specific items of plumbing and patients were being infected during hydrotherapy [76]. Measures included deep cleaning and replacing the colonised plumbing parts. Another WGS study found that a hard-to-resolve outbreak of methicillin-resistant *Staphylococcus aureus* (MRSA) on a neonatal baby unit was caused by an asymptomatic member of staff once they had been decolonised no further MRSA cases occurred [75].

WGS has also been used to demonstrate sources and transmission of infection, information that is useful in informing infection control measures and policy. A study on *Clostridium difficile* infections in Oxfordshire hospitals over 3.5 years showed many diverse sources of infection, with only 35% of cases in hospitals being due to transmission from symptomatic patients.

Other sources of infection included strains circulating in the community and asymptomatic patients [168]. Prospective surveillance using WGS of MRSA in hospitals and the community showed different transmission routes involving hospital contacts, community contacts, or both [169].

A WGS investigation of multi-drug resistant *E. coli* in a long-term care facility, showed transmission within the facility but also that cases were linked to those found in local hospitals [170].

These examples and others demonstrate the benefits of using WGS as an infection control tool:

- **Responsive use:** if conventional methods have not determined the cause of an infectious outbreak, WGS can help to identify the source and/or route of transmission
- **Surveillance:** this can contribute to earlier detection of outbreaks, monitoring infection control practice and refinement of infection control policy
- **Determining if there is an outbreak:** WGS can help determine whether cases are related, if not, an outbreak can be excluded; benefits include more focused targeting of infection control resources
- **Swifter outbreak resolution:** WGS can determine the source of outbreaks in cases where conventional methods cannot
- **Better targeting of infection control measures:** more accurate identification of the source and transmission of infections can lead to more targeted response measures e.g. cleaning focused on particular areas or equipment
- **Better informed infection control policy:** knowing when there has not been a failure of infection control thereby avoiding unnecessary follow-up measures

Considerations for NHS England

WGS is recognised as a useful tool for outbreak management for a range of pathogens. For hospital-based surveillance and outbreak investigations that may fall outside the national public health function remit of PHE, NHS England could consider:

1. NHS capacity for, or access to, pathogen WGS, for example via agreements with PHE or by utilising current/future NHS WGS provision, for resolving challenging hospital outbreaks and/or for surveillance.
2. Ensure collection of data and knowledge about which types of outbreaks benefit from a WGS approach – WGS is currently used on a case-by-case basis, and often retrospectively. More data are needed on which outbreaks would benefit from a WGS approach; collaboration with PHE to collect these data might be required, given their expertise in this area.
3. Following on from (2), how and when WGS services might be accessed – e.g. the criteria that must be met to confirm use of WGS to resolve an outbreak.
4. How WGS might be used for surveillance, and for which pathogens.

The utility of pathogen WGS in resolving challenging outbreaks within the health system has been demonstrated, the challenge for the health system is to determine how WGS can be incorporated into infection control efforts when appropriate and how the health system can access these services.

5.4 Regenerative medicine

Regenerative medicines (RM) are treatments which seek to replace, repair or regenerate the body's cells, tissues and organs. In this analysis two key areas of RM – gene therapies (including gene editing) and stem cell therapies – are discussed in further detail. To clarify the terms used to describe different aspects of RM, a definitions table has been included at the end of this section alongside example therapies (see page 124).

The terms gene and genome are often used interchangeably in the context of gene/genome therapy and editing; for simplicity, the word gene is used for the duration of this section.

How can regenerative medicine deliver personalised medicine?

RM approaches have shown great potential and remain highly promising; a large number of therapies are in development but so far few have made it into routine care. RM can help to deliver personalised medicine by utilising the patient's own cells (autologous treatment) and systems, or donor cells (allogeneic treatment) specifically customised for the patient, to achieve clinical improvement with reduced risk of tissue rejection.

Both stem cell and gene therapies offer a broad range of opportunities for advancement and novel treatments in healthcare, particularly for the management of rare diseases for which there may be no other available treatment. Many new RM approaches use one or more innovative approaches, for example stem cells and gene therapy; as such, consideration needs to be given to how the classification and regulation of these therapies is managed. There are several potential advantages of RM over conventional treatments, including:

- Potential curative treatments for conditions for which there is an unmet clinical need
- The potential replacement of expensive long-term treatment plans with one-off or infrequent interventions leading to long-term cost saving for health services and relief/respite from taxing regimes for patients
- Reduced risk of tissue rejection where autologous treatments are used instead of transplants

While rare disease treatments provide a showcase of the potential of RM therapies, broader patient benefit will also be seen from the delivery of therapies for more common but severe conditions such as some forms of cancer.

The current state of implementation: stem cell therapy

A number of stem cell-based treatments, such as haematopoietic stem cell transplantation (HSCT) for leukaemia, lymphoma and some inherited blood disorders have been in routine use for decades. Novel HSCT treatments are also being trialled for the treatment of multiple sclerosis [171], stiff person syndrome [172] and progressive encephalomyelitis (albeit under strict circumstances) within the NHS by Sheffield Teaching Hospitals NHS Foundation Trust alongside a handful of other centres [173].

Recent interim results from the MS trial highlight notable improvements in patients that underwent HSCT, above and beyond those seen in the drug-only group [174]. Clinical trials are ongoing.

There are currently two stem cell-based advanced therapy medicinal products (ATMPs) that have been approved by NICE:

- Holoclar utilises limbal stem cells to repair the cornea following injury. It costs approximately £90k per treatment
- Strimvelis uses both stem cells and gene therapy for the treatment of the adenosine deaminase specific form of severe combined immunodeficiency (ADA-SCID). It costs £500k per treatment and is administered in Italy where the treatment centre is based. It is expected that up to three patients per year will be eligible [175]

Another stem cell technology in use in some NHS facilities is the medical device Celution, which processes a patient's own adipose tissue to enrich for stem cells in the sample. This is then used in tissue reconstruction following breast cancer surgery. Evidence suggests cost-savings over other tissue restoration techniques [80] and trials have reported high patient satisfaction [176, 177]. Concerns have been raised about the lack of controlled comparison with conventional techniques such as synthetic implants and fat grafting [178]. Issues with initial investment by clinical facilities and lack of NICE recommendation have been cited as reasons for slow uptake of this technology [179, 180].

The current state of implementation: gene therapy

The use of gene therapies in the UK is currently limited to small-scale applications and trials, several of which have recently yielded promising results. The principle of gene therapy is to establish gene function in affected cells, tissues, or individuals by introducing a functional gene copy, usually using a specially adapted virus for delivery. Gene editing utilises one of three gene editing techniques (Table 5.3) to alter a specific site of the patient genome or genome of particular cells. This may include insertions, deletions or other alterations in the genome.

Gene therapy research and development is highly active. Results from successful gene therapy clinical trials in haemophilia were reported in December 2017: treated patients were subsequently able to make their own clotting factor, effectively eliminating haemophilia symptoms [83, 181]. These treatments now require long-term examination of safety and efficacy.

Gene therapy approaches are also being explored for sickle cell disease and β-thalassemia [182–184] (with some at an advanced stage of development), and a substantial number of trials are being conducted into gene therapy use in various conditions including MS, Huntington's disease and Duchenne Muscular Dystrophy; these are in the early stages [185–187]. In 2017, the FDA approved its first three gene therapies for clinical use including one *in vivo* gene therapy, Luxturna, which is used for the treatment of a rare form of inherited vision loss [188].

Gene editing (using the techniques outlined above) in humans is limited; the first *in vivo* gene editing clinical trial was reported in November 2017 for the treatment of Hunter's Syndrome [82] and currently has a single participant.

Table 5.3: Gene editing technologies

Editing technique	Pros & cons	Treatment examples
ZFN - Zinc finger nucleases	**Pros** • Rapid editing **Cons** • Can be difficult and relatively expensive to design • Some off-target effects	Some instances of *ex vivo* editing in trials; a single *in vivo* trial for treatment of Hunter's Syndrome [82]
TALEN - Transcription activator-like effector nucleases	**Pros** • Cheaper and easier than ZFNs • Relatively accurate **Cons** • No multiplexing capability	Used to provide additional edits (*ex vivo*) to CAR-T cells for the treatment of two patients in UK [189]
CRISPR/Cas9 - Clustered regularly interspaced short palindromic repeats/associated protein 9	**Pros** • Cheap and easy target design • Multiplex edits **Cons** • Uncertainty around off-target effects	Currently research only Recent submission to EMA for commencement of human trials using CRISPR for the treatment of β-thalassemia [190]

Gene therapy in cancer treatment

Chimeric antigen receptor T-cell (CAR-T) therapies involve the extraction and genetic alteration of T cells from the patient or a donor to express specific antigen receptors on the cell surface. These chimeric antigen receptors allow the T cells to detect and attack targeted tumour cells. CAR-T therapies are potentially highly flexible, allowing for the tailoring of treatments to treat a range of cancers.

In 2017, two CAR-T cell therapies were granted approval for use by the FDA:

- Kymriah for acute lymphoblastic leukaemia (ALL) in children and young adults [191]
- Yescarta for the treatment of diffuse large B-cell lymphoma (DLBCL) in adults [192]

In November 2017, Novartis submitted Kymriah to the EMA for approval for the treatment of both ALL in adults and children, and DLBCL in adults (for which it submitted to the FDA at the end of October) [193]. An off the shelf allogeneic CAR-T therapy was used in the successful treatment of acute lymphoblastic lymphoma in two infants in the UK [189]. A number of other CAR-T based therapies are in advanced stages of development [194].

Oncolytic virus cancer therapy, Imlygic, gained NICE approval for the treatment of some metastatic melanomas in 2016 [195] and is being trialled in the UK for use in head and neck cancers. The treatment utilises a genetically modified herpes simplex virus that attacks cancer cells and also stimulates the body's own immune system to attack the cancer [196].

One-off gene therapy uses

In the UK and further afield, there have also been isolated applications of gene therapies. Examples of these include the first example of *in vivo* gene editing in a patient with Hunter syndrome in the US [82], gene-edited CAR-T treatment of two infants with leukaemia in the UK [189], and the treatment of the skin disease epidermolysis bullosa in a single patient through gene editing and tissue growth in Germany [197].

Policy and development in regenerative medicine

Current regulation of regenerative medicines

Regenerative medicines are subject to a range of regulatory pathways that differ depending on the techniques and materials used, for example viruses or human cells/tissues, and how many patients might benefit from the therapy. Some, but not all, RM products are classed as Advanced Therapy Medicinal Products (ATMPs) [198]. ATMP is a regulatory construct that includes therapies that utilise viable cells or tissues for human medicinal use dependent upon the extent and character of manipulation applied.

The Medicines and Healthcare products Regulatory Agency and Human Tissue Authority contribute to a one stop shop regulatory advice service, called The Regulatory Advice Service for Regenerative Medicine (RASRM) that brings together these two bodies plus the Human Fertilisation and Embryology Authority, the Health Research Authority, and other specialist bodies [199]. The service consolidates regulatory advice for RM from these four bodies. One-off uses for novel/unlicensed therapies may be permitted under the Hospital Exemption (EU) and Specials Exemption (UK).

Given the expected increase in the availability of regenerative medicines, serious consideration will need to be given as to whether the current regulatory frameworks continue to serve their purpose.

Policy development in regenerative medicine

The availability of RM therapies fits with the government's broader goals of advancing personalised medicine, and RM has not escaped the notice of policy advisors. Several examinations of the current and future status of RM have been conducted, with subsequent recommendations made for advancing development, manufacture and distribution.

These include:

- MRC regenerative medicine strategy (March 2012)
- Department of Health and Regenerative Medicine Expert Group report (March 2015)
- House of Commons Science and Technology Committee report on regenerative medicine (Fifteenth Report of Session 2016–17)

Progress has been made in several areas, including investment of funds committed to manufacturing of RM and development of specialised treatment centres (see below), however slower progress is being made in other areas.

Technology and application development in regenerative medicine

RM is an international collaborative enterprise and global investment in the area is substantial [200], with the commercial sector playing a significant role in the development and implementation of RM [71]. The UK Cell and Gene Therapy Catapult (CGTC) recently announced a memorandum of cooperation between the UK and the Kanagawa Prefecture of Japan, specifically aimed at advancing medical research and development in promising areas, including RM [201].

In the UK, the CGTC highlights that around 40% of clinical trials in the UK are sponsored by industry, and the size of the UK's good manufacturing practice licensed manufacturing has increased by nearly 20% every year since 2012 with an additional £12M awarded through the Industrial Strategy Challenge Fund for the UK CGTC Stevenage-based manufacturing facility [70]. There are also public and private providers of cell and tissue storage facilities, operating under different models [202].

A number of companies (especially in the US) are developing CRISPR-based editing technologies for disease treatment [203–205]. These therapies have yet to reach human trials, however Crispr Therapeutics (based in Switzerland) recently submitted an application to begin human trials of their therapy for β-thalassemia sickle cell disease (CTX001) to European regulators [190].

Establishment of treatment centres in the UK

In 2017, Innovate UK announced a £30M funding competition for the establishment or development of three advanced therapy centres across the UK as part of the government's Industrial Strategy Challenge Fund. The competition invited applications from collaborative ventures (combining business, hospitals, academic establishments and others).

The competition results were announced in January 2018, with successful centres distributed across the country with network focal points in Birmingham, Newcastle and Manchester [206–209]. Additional funding has also been allocated for the manufacture of enabling technologies such as viral vectors for the delivery of gene therapies to cells [209, 210].

Challenges affecting uptake of regenerative medicines and considerations to support the implementation of regenerative medicine in the UK

The field of regenerative medicines is large, diverse and complex. RM has the potential to impact on many different areas of clinical practice so one of the major challenges facing the implementation of RM into the health system is to build a comprehensive and coherent strategy to manage the issues that affect the establishment of RM into routine practice. RM is an ongoing policy priority and much work has already been done to consider how the implementation of RM can be supported.

Key consideration: Routine use of RM will require the recommendations made by the Regenerative Medicine Expert Group and the House of Commons Science and Technology Committee enquiry on regenerative medicine to be fully addressed. Progress towards these recommendations would benefit from a national coordinated approach, with designated leadership who are appropriately equipped to harmonise and drive forward efforts for advancing RM in the UK.

Building and considering the evidence base

There are inherent difficulties in building a sufficient evidence base for the efficacy of many regenerative medicines, especially given their biologically variable and patient-specific nature, and in many cases low patient numbers. Long term follow up is needed to demonstrate safety and longevity of therapies, however, the need for this evidence should be balanced against the need to explore therapeutic options in patients with rare and life-limiting conditions. The conventional randomised clinical trial model does not work as well for RM given low patient numbers for each treatment type.

Key consideration: The health system should consider new models of evidence gathering in support of therapies for rare conditions with low patient numbers, right down to 'n of 1' therapies. The volume and type of evidence required should be considered in light of the cost/benefit of the therapy, number of patients who benefit and how often evidence should be reassessed as patients undergo long-term follow up.

Support for therapy development and reimbursement strategies

Development of therapies is high risk for companies since treatments are costly to develop and there is no guarantee of reimbursement. Since 2009, nine ATMPs have been approved by the EMA for use in Europe. However, several of these have now been withdrawn, due to issues with commercialisation and cost leading to poor uptake in the clinic [81, 211]. A summary of these products is given in Table 5.5.

Lack of evidence of cost-effectiveness can make it difficult for national healthcare agencies to fund RM therapies for patient use [212]. Even with this evidence, high upfront costs may delay adoption. Alternative reimbursement strategies would likely encourage uptake of costly RM therapies.

In collaboration with the University of York, NICE conducted a mock appraisal of CAR-T therapy to determine whether appraisal systems were fit-for-purpose in the case of RM. The report highlighted the potential value of monthly payment plans for RM products (lifetime leasing method), managed entry agreements and risk mediation with manufacturers in reducing upfront costs and mediating financial risk for the NHS [213].

Key consideration: The health system should consider new models of reimbursement that support end-stage therapy development and testing through clinical trials as a way of balancing costs and risks for both manufacturer and the health system, while ensuring there is minimal delay in patients benefitting from proven innovative therapies.

Regulation of regenerative medicines

Owing to some extent to the biological complexity of RM products, the regulatory procedures surrounding their application in the UK are complex and a source of confusion for researchers, commercial bodies, manufacturers and practitioners [71, 212]. This may cause delay in the development and evaluation of therapies.

Treatments such as Holoclar have been allocated orphan medicinal product (OMP) status by the EMA, granting ten year market exclusivity and fee reduction for protocol assistance (including scientific advice for trial or study design) following approval [214]. Treatments may remain with OMP status for quite some time, which is advantageous in terms of allowing swift patient access, however, this may also suppress the development of alternative treatments and/or delay their implementation.

Key consideration: Clear regulatory processes are required if the UK is to effectively adopt beneficial RM treatments, including clear regulatory definitions of different treatments. The RASRM one-stop shop is an example of how a coordinated regulatory approach can be realised, this approach should be assessed to determine if it is meeting the current needs of the RM landscape. Other regulatory constructs such as specials exemption or OMP status should be reviewed to determine if and how they can best respond to developments in RM and encourage inward investment in RM in the UK.

Manufacture of regenerative medicines

Initiatives are already in place to support the manufacturing of RM products in the UK which will be of long-term benefit to the UK. However given the speed of developments, shortages of some of the products required for delivery of RM, such as viral vectors, are an ongoing concern and have been seen in other countries [215]. Support for manufacturing is essential given that processes are complex and require stringent quality control and assurance systems. In addition, the health system will have to carefully balance production with demand, since many products have a limited shelf life and cannot be stored longer term.

Key consideration: Manufacturing infrastructure should be flexible and able to respond to the emergence of new technologies and demand for products, ensuring that there is not a delay in research into RM or in the delivery of RM therapies to the health system.

Health system delivery of regenerative medicine

There is already an extensive infrastructure in place within the NHS that supports the delivery of stem cell transplants for haematological malignancies and other conditions. The health system therefore already has expertise in the storing, handling and delivery of cell and tissue products which can be utilised to support the delivery of certain RM therapies, such as CAR-T therapy for cancers. In other clinical specialities, however, consideration needs to be given as to how to meet the logistical challenges of accessing, storing and delivering RM, training the workforce in its use and considering the interactions between the different clinical specialities required to deliver a RM e.g. in the case of Holoclar: ophthalmology and surgery.

Key consideration: The health system should consider how to take advantage of current infrastructure and expertise to deliver some RM therapies, and how to support and strengthen these centres.

Key consideration: The health system should seek to ensure the development and/or maintenance of an appropriate skill base, in addition to ensuring that physicians are adequately trained to understand, adopt and apply RM. Surgical and medical expertise are required that complement emerging RM therapies in different clinical specialities.

Key consideration: Given the logistical challenges associated with live cell and tissue treatments, the geographic distribution of centres of excellence in RM should be considered in order to achieve equitable access, with consideration of specific population concerns, e.g. sickle cell treatments in areas where population demographics result in greater demand. The establishment of three new ATTCs across the country will help to make RM more accessible, provided appropriate expertise can be built-upon at these locations [209].

Conclusions

The increased availability of RM therapies fits with the broader goal of advancing personalised medicine. A number of the regenerative medicine treatments offer potentially curative or long-term treatments for chronic diseases for which current therapies only provide short-term or symptom-only relief, and the number of such therapies is likely to increase in the next three years.

RM ranges in application from large-scale oncology treatments to small-scale and trial-based rare disease treatments, and accommodating these within current healthcare structures is a challenge that is being undertaken globally. Some RM therapies are available here and now, and a number of pioneering techniques may present a credible evidence base within the next couple of years.

In order to take full advantage of RM in the clinic, continued reassessment of regulatory structures, adapted methods for reimbursement, and the ability for clinics to invest in initially costly but cost saving equipment are required to ensure beneficial treatments are successfully implemented. An appropriately trained and prepared workforce with access to facilities where they are needed by patients will also speed access to RM for those who need it.

Continued long-term infrastructure investment is required with frequent review of upcoming treatments in clinical trials to ensure the UK is best placed for this quickly advancing area of healthcare. All these factors need to be addressed if the UK is to build on its strong research base and progress in the implementation of RM clinical services beyond the research setting.

Table 5.4: Regenerative medicine definitions

	Description	Examples
Gene therapy	The insertion of genetic information into one or more cells, usually by viral vector. Sometimes used as an umbrella term for both gene therapy and gene editing	• Haemophilia A trial (UK) • RPE65 trial for retinal degenerative disease • Strimvelis for ADA-SCID (gene therapy applied to multipotent cells)
Gene editing	Alteration of an individual's genome in one or more cells through the delivery of gene editing tools - ZFN, TALEN, or CRISPR. Can include deletion, alteration or insertion	• Off the shelf *ex vivo* CAR-T therapy - individual cases (two infants with leukaemia) permitted under hospitals/specials exemptions in UK • Single person trial of *in vivo* gene editing for treatment of Hunter Syndrome in the US
Stem cell therapy	Therapies that either specifically target stem cells or utilise them as a medicinal product	• Some treatments have been in use for decades e.g. HSCT for leukaemia • Novel HSCT use in multiple sclerosis and stiff person syndrome • Holoclar for the rare condition limbal stem cell deficiency • Celution for partial breast reconstruction
In vivo/ex vivo	Refers to whether the procedure (chiefly cell editing) is conducted inside or outside of, respectively, the patient's body	• *In vivo* example: Single person trial of gene editing for treatment of Hunter Syndrome in the US utilises ZFN injection • *Ex vivo* example: During CAR-T therapy for cancer, cells are altered to express antigen receptors on their surface; this takes place outside of the body
Allogeneic/ autologous	Refers to whether the cells of a healthy donor or a sample of the patient's own cells are used for the treatment	• Allogeneic: Healthy donor cells are used in treatment. Batches are 'off-the-shelf' and often used to treat many patients • Autologous: The patient's own cells are used in treatment. Used to treat one individual
Advanced therapy medicinal product (ATMP)	EU regulatory construct applicable to some medicines that use cells, genes or tissues	• The classification is complex and requires consultation with appropriate advisory bodies to determine for each product • Strimvelis and Holoclar are both classed as ATMPs • Celution is classed as a 'medical device' not an ATMP as cell/gene alteration or culture is not involved

Table 5.5: Advanced Therapy Medicinal Products approved for use by the European Medicines Agency

Company	Headquarters	Trade name	Disease/condition	EMA public classification	EMA approval	NICE recommendation
Tigenix/Takeda	Leuven, Belgium	ChondroCelect	Complex perianal fistulas	Tissue-engineered product	Oct 2009 - retracted	None published
UniQure NV	Netherlands	Glybera	Lipoprotein lipase deficiency	Gene therapy	Jul 2012 - retracted	None published
Vericel	US	MACI	Cartilage defects of the knee	Tissue-engineered product	Jun 2013 - suspended	No - ACI reviewed in October 2017*[216]
Dendreon Pharmaceuticals	US	Provenge	Metastatic castrate resistant prostate cancer	Somatic cell therapy	Sep 2013 - retracted	Appraisal withdrawn [217]
Chiesi/Holostem Terapie Avanzate	Manchester, UK	Holoclar	Limbal stem-cell deficiency (caused by eye burns)	Tissue-engineered product	Feb 2015	Yes† - 16 Aug 2017 [218]
Amgen Europe BV	California, US	Imlygic	Melanoma	Gene therapy	Dec 2015	Yes† - 28 Sep 2016 [195]
GlaxoSmithKline	Brentford, UK	Strimvelis	ADA-SCID - Severe combined immunodeficiency due to adenosine deaminase deficiency	Gene therapy	May 2016	Yes† - 07 Feb 2018 [175]
MolMed SpA	Milan, Italy	Zalmoxis	Add-on to HSCT for blood cancers - aid in restoration of immune system	Somatic cell therapy	Aug 2016	No review published
Co Don AG	Germany	Spherox	Cartilage defects of the knee	Tissue-engineered product	Jul 2017	Yes† - 07 Mar 2018 [216]

*Autologous chondrocyte implantation (ACI) provided by the OsCell John Charnley Laboratory permitted under MHRA's hospitals exemption from ATMP regulation. The technology appraisal conducted by NICE is only applicable to technologies with contemporary marketing authorisation or MHRA exemption.

† Criteria for treatment recommendation are given in the NICE guidance

5.5 Transcriptomics

This analysis covers the current and potential upcoming clinical use of RNA-based gene expression profiling (GEP) diagnostics and prognostics.

RNA-based GEP tests examine levels of RNA biomarkers (the vast majority utilising messenger RNA) and may be used to help patients and clinicians make decisions about treatment, including likely prognosis and drug or therapy selection. The tests utilise one of RNA counting, qRT-PCR, microarray or RNA-sequencing to examine gene expression of a pre-determined set of genes. Some panels also exist for the purpose of aiding diagnosis.

A number of the tests available have been developed for treatment stratification and prognosis in subsets of breast cancer, for which Oncotype DX is currently available on the NHS, although the associated NICE guidance is currently under review [219].

Why use gene expression profiling tests to personalise patient care?

Gene expression profiling may be a useful tool for aiding the personalisation of treatment by providing further patient or disease stratification and additional diagnostic/prognostic power. Potential benefits over or alongside conventional physiological, histological, nomogram (prediction tool) and single-marker based assessments include:

- Extra information for prognosis, treatment planning and management including the selection of drugs and therapies beyond that provided by current practice, resulting in a greater personalisation of and more directed treatment for each patient
- Provision of additional information for patients and additional evidence for clinicians to aid decision making on whether to undergo or to recommend potentially life-saving but otherwise toxic treatment regimens
- Potential cost saving in situations where a GEP test determines that an expensive therapy is unlikely to benefit a patient
- A potentially broad range of RNA-based diagnostic and prognostic applications, in areas such as infectious disease, oncology, and depression

The current state of implementation

GEP tests have been developed across a broad range of conditions and diseases. GEP tests currently in use or in latter stages of assessment in UK healthcare are exclusively for use as adjuncts in cancer treatment. The majority of these are for the stratification of treatment, or assessment of recurrence risk, in breast cancer.

Most tests can be performed on formalin-fixed paraffin-embedded (FFPE) tumour biopsy samples, utilising tumour tissue removed during surgery rather than requiring a patient to undergo an additional biopsy. Analysis is primarily performed in manufacturer approved laboratories, with some tests offering the option of partial off-site analysis at a reduced price.

Gene expression profiling tests for oncology

In 2013, NICE evaluated four tumour-profiling tests for their use in treatment stratification for breast cancer patients [22, 220]. These tests were IHC4, MammaPrint, Mammostrat, and Oncotype DX. Oncotype DX and MammaPrint are RNA-based and use qRT-PCR and microarray technology respectively, to examine expression profiles for subsets of genes in order to assess individual patient risk of disease progression or recurrence.

Only one of these tests, Oncotype DX, was subsequently recommended for clinical use. These tests are only suitable for use in a subset of patients diagnosed with breast cancer.

Oncotype DX is a qRT-PCR based breast cancer prognostic tool that assesses cancer recurrence risk in patients with lymph node negative, oestrogen receptor (ER) positive and human epidermal growth factor receptor 2 (HER2) negative breast cancer by examining the expression activity of sixteen associated genes, plus five controls, alongside other risk information. Currently all samples are sent to a laboratory in the United States for analysis. A review of the literature shows that Oncotype DX has been associated with notable cost saving through reduced chemotherapy use [221–223]; patients receiving a low risk score may be spared chemotherapy.

Recent results from the large TailorX trial based in the US suggested that women receiving intermediate risk scores from the test are also unlikely to benefit from chemotherapy [224]; however, there were some limitations to the study and the above conclusion only held up for older patients.

There is still limited evidence of the test's major value in prognosis beyond that already provided by prediction tools such as 'PREDICT', a mathematical model that uses histopathological data to determine the likely outcomes and benefits of therapies to all patients with breast cancer.

Approved by NICE in September 2013 and now available on the NHS, Oncotype DX is currently under NICE review and recent draft recommendations suggest that the test will retain its recommendation and both Endopredict and Prosigna will be recommended for the first time, with the condition that, under a data collection agreement with NICE, test data is made available to the National Cancer Registration and Analysis Service. The expected publication date of the updated guidance is 12th September 2018 [219].

Several additional tests have been the subject of NICE Medtech Innovation Briefings [225–227]; however in most cases, an improved evidence base is recommended or sought before reliable evaluations of clinical utility can be made. A recent briefing on the breast cancer subtype test, MammaTyper, stated that there is good evidence for clinical utility beyond that of current immunohistochemistry based testing, with consistency of result interpretation cited as a particular advantage [227].

Prostate cancer treatment stratification GEP tests that examine indicators of cancer aggressiveness in individual patients are also being developed or marketed. A number of tests (such as Prolaris, Oncotype DX Prostate, and Decipher) have been evaluated in the US for clinical and analytical validity. These remain as investigational research tools, owing to a lack of evidence demonstrating improved health outcomes in patients.

Tests vary in terms of the patient groups for which they have been developed e.g. tests such as FDA-cleared companion diagnostic MammaPrint could offer additional recurrence risk information for patients with breast cancers for whom Oncotype DX is unsuitable. A number of clinical trials are taking place assessing GEP tests, examples are given below (Table 5.6).

Table 5.6: Examples of ongoing clinical trials investigating the use of GEP tests in treatment stratification (source: ClinicalTrials.gov)

ClinicalTrials.gov Identifier	Trial Title
NCT03152448	Prospective Prolaris Value and Efficacy (P-PROVE)
NCT01479101	NBRST: Prospective Neo-adjuvant REGISTRY Trial (NBRST)
NCT01501487	MINT I Multi- Institutional Neo-adjuvant Therapy MammaPrint Project I (MINT)
NCT02773004	Prospective Study Assessing EndoPredict® Genomic Test Impact on Shared Decision of Adjuvant Chemotherapy in Patients with ER-positive, HER2-negative Early Breast Cancer (ADENDOM)
NCT03290508	Long-term Study to Evaluate and Clinical Outcomes in Patients With Favorable Intermediate Risk Localized Prostate Cancer
NCT00310180	Hormone Therapy With or Without Combination Chemotherapy in Treating Women Who Have Undergone Surgery for Node-Negative Breast Cancer (The TAILORx Trial) (TAILORx)

Other large-scale studies include the PONDx programme, a multi-centre study evaluating treatment selection outcomes of Oncotype DX Recurrence Score use in France, where the test is available through an early-access to health innovations scheme (RiHN). Results to date show notable reductions in chemo-hormonotherapy use following Oncotype assessment; however no information on patient survival outcomes has been provided [228].

Metastatic cancer and cancers of unknown primary testing

A selection of GEP tests and tests with gene expression components exist for the identification of tissue of origin and treatment stratification in metastatic cancers and suspected cancer of unknown primary (CUP).

Examples of these tests are:

- Oncofocus, a DNA- and RNA-sequencing test from a UK company that examines a panel of around 500 genes and has broader applications in oncology as a drug selection test
- Caris Molecular Intelligence, a multi-omic (DNA, RNA, and protein) tumour profiling system for guiding the management of locally advanced metastatic or rare cancers such as CUP
- Tissue of Origin, an FDA-cleared microarray-based GEP test covering around 2000 genes for the assessment of cancer origin.

Current NICE guidelines (published in July 2010 and reviewed March 2017) state explicitly that gene-expression-based profiling is not to be used to identify primary tumours in patients with provisional CUP or in guiding treatment decisions for patients with confirmed CUP [229].

None of these tests are available on the NHS, but can be purchased by the patient.

Gene expression profiling tests for other conditions

Outside of cancer treatment stratification, gene expression panels are being developed for use in several physical and mental health disorders [17, 18, 230]. One such panel is the age/sex/gene expression score (ASGES)/CardioDX gene expression test for use in the early detection of patients with suspected obstructive coronary artery disease.

A study published in April 2017 examined the utility of the ASGES/CardioDX gene expression test for this purpose [18]. Significant differences were found regarding clinical outcomes for patients categorised as high and low risk following testing, however, the real prognostic value of the test appears limited, and clinical benefit is not yet evident.

Several systems are being developed in the private sector, primarily by companies based outside the UK. As knowledge develops internationally, GEP tests are beginning to overlap with other innovative areas of health.

Several multi-omics tests are in advanced stages of development, liquid (urine or blood) biopsy RNA-based tests are beginning to emerge [231–233] and companies are investigating the use of artificial intelligence (AI) to support the discovery of disease outcome links with molecular diagnostics results [233, 234].

Policy and funding actions supporting GEP test development

In January 2018, Genomic Expression (a US-based medical diagnostics company) and partners received €3.7 Million in funding from the EU Horizon 2020 project for the advancement and assessment of its OneRNA platform for diagnosis, treatment selection and recurrence risk assessment in cancer, under the project title OneRNA4Bladder [235].

OneRNA differs from current GEP panels in that its technology has moved from microarray to RNA sequencing based analysis and utilises an alternative sample preparation method. It also covers a relatively large number of genes. This system potentially offers flexibility through a broader range of disease applications than other panels, however, as with others, it has yet to be proven.

The establishment of a national genomic laboratory infrastructure (Chapter 2) could have an impact on the delivery of transcriptomics by changing the accessibility of sequencing and other RNA analysis infrastructure, and standardisation of referral and testing practices. In time, this may facilitate the development of in-house RNA-based diagnostics dependent upon effective knowledge sharing and appropriate reviews of biomarker evidence.

System implementation challenges and considerations for action

A number of GEP and RNA-based diagnostics appear to hold potential for the stratification of treatment for conditions such as breast cancer. Although barriers exist to the effective uptake of GEP tests in routine healthcare, there are a number of steps that may be taken to prepare for the adoption of new RNA-based molecular diagnostics in these fields, should supporting evidence come to fruition.

Collection and assessment of appropriate evidence

The most significant challenge affecting the implementation of many commercially available GEP tests is the lack of evidence of clinical benefit and cost effectiveness. While many of the tests have a fairly substantial evidence base, these may be insufficient due to risk of bias, lack of controls or other failings in some trial data. In particular there is little information available about long term patient health outcomes, or of the utility of these tests beyond that provided by current techniques. Ongoing clinical trials should help address these evidence gaps.

Although the potential application of GEP tests as a whole is broad, the application area for individual tests is often quite limited. There is some concern about mission creep, where individual tests may start being used in similar clinical indications for which there is little or no supporting evidence for their use.

Key consideration: The results from ongoing clinical trials should be considered if/when evidence emerges in support of the use of GEP tests. The cautious and considered utilisation of early access schemes (such as PONDx in France) may help in terms of gathering evidence on clinical effectiveness. The aforementioned new draft guidelines from NICE state that test data collected from the future use of any recommended GEP in breast cancer prognosis and treatment stratification must be submitted to the National Cancer Registration and Analysis Service for further assessment of test data and its link to chemotherapy use, recurrence risk and survival outcomes [219]. This will be beneficial to the further assessment of the tests.

Key consideration: Due to the large numbers of tests being developed, the healthcare system should consider a flexible approach to panel adoption and how to allow for timely review of updated evidence on current tests and evidence in support of new tests, to determine which tests should be adopted. As foundational knowledge of the transcriptome grows, the combination of genes included within panels should evolve and recommendations for individual panel use will change over time.

Commercial development of GEP tests

Panel tests are mostly being developed by commercial entities, and as a result are protected as intellectual property, making it difficult to bring diagnostics in-house. Generating panel based tests in-house from scratch is challenging due to the extensive costs and efforts required for the identification of and demonstration of clinical utility of markers for gene panels. Looking forward however, the establishment of the national genomics laboratory infrastructure, could provide an opportunity for the investigation of RNA and biomarker-disease association as evidence evolves, and infrastructure for carrying out gene expression and data analysis become more accessible.

Key consideration: The health system should consider regular review of advances in transcriptomics technologies and the optimal approach for delivering testing via the Genomic Laboratory Hubs, either in-house or via commercial providers.

The impact on patients of using GEP testing

Many commercial tests are conducted off-site and require samples be sent to manufacturer-specified laboratories, this requires additional logistical considerations for clinicians and pathologists in terms of collecting and processing samples for shipment. Some providers offer the option for part of the process to be conducted in the laboratory seeking the test which results in a reduced cost per test [226].

This may require initial investment in infrastructure in terms of set-up costs and the processing of samples. Most external laboratories offering tests require FFPE samples, which is currently the standard method of processing biopsy samples.

Tests requiring fresh or fresh-frozen samples (-80°C for preservation of RNA), require more specialist treatment when collected, and standards for sample collection may change with time. The development of pathways by the 100,000 Genomes Project to collect fresh-frozen tumour samples will have an impact on the health system's ability to manage samples of this type, however pathways for sample collection and processing will differ between different clinical specialities.

Performing GEP tests can add additional time to a patient's treatment, creating concern for patients. Oncotype DX testing can take 2–3 weeks from collection of the sample to review of the results with the patient (NHS Consultant, personal communication). Whilst some of this can be attributed to the process of sample testing, analysis (performed in the United States), and result retrieval, pathology processing may also be a source of delay. Although the sample is retrieved during standard surgical procedures, the processing and delivery of these samples has to be performed efficiently.

Key consideration: The NHS could consider whether to seek agreements with manufacturers whereby one or more parts of the analysis are internalised to the laboratory ordering the test.

Key consideration: The health system should consider how to manage the different sample requirements of RNA-based tests in a timely manner, and how it might make best use of the pathways established to collect fresh tissue (as part of 100,000 Genomes Project) for clinical specialities where collecting this sample type is not standard practice.

Foundational knowledge of the transcriptome

Understanding of the genome and the transcriptome are continually expanding; nevertheless, this exploration is also highlighting further areas where more research is needed. Our understanding of the action of non-protein-coding RNAs is still very much in the primary research stages, and is not without controversy. As such, our ability to draw clinical conclusions from much of the transcriptome is still some way off.

Conclusions

Transcriptomics is a promising technology that will have a future role to play in the personalisation of medicine. GEP tests are already in use, with the majority of tests under review designed as tools for prognosis and treatment stratification in subsets of breast cancer. Their suitability is currently under review as questions surrounding patient outcomes and cost-effectiveness remain to be answered; evidence of real clinical utility is required to support their routine use in healthcare. The health system should therefore be ready to respond to evidence as and when it emerges, and consider how existing laboratory genomics infrastructure can be developed to support the timely implementation of testing when appropriate.

5.6 Advanced image analysis

Medical images assist medical professionals to make a diagnosis, recommend treatment and monitor disease progression. These images can be captured using radiology approaches such as X-rays, magnetic resonance and computed tomography where the internal structures of an individual are scanned, or by histopathology approaches that examine tissue sections or blood samples on a glass slide to study cellular and subcellular markers. Image interpretation is carried out by radiologists and pathologists.

There is a growing interest in novel approaches to aid medical image analysis because:

- A recognised challenge is that despite guidelines, there can be inter and intra-observer variability as many features are open to interpretation [236, 237]
- Experts currently have limited tools to aid them in these analyses
- There is a national shortage of radiologists and pathologists
- There are increasing numbers of images to be analysed
- There is a growing complexity of analysis given the increasing array of markers to be assessed

As described in Chapter 4, artificial intelligence (AI) approaches have the potential to transform medical image analysis –with both radiology and histopathology as promising areas for AI application [238]. However digitisation of medical images and digital infrastructure is a critical prerequisite to achieving this potential. Radiological images are already predominantly captured in a digital format. In contrast, only a few pathology departments in the NHS are utilising digital approaches for capturing and analysing histopathology slides. This is due to the high initial start-up equipment and IT investments required, the additional workflow step to convert a physical glass slide into a digital image, uncertainty about the validity of digitised workflows, and technology variability [239, 240].

However, evidence of the value of digital pathology (DP) is mounting, leading a number of hospitals within the NHS and many internationally to explore the use of and adopt this technology.

The health system-wide deployment of DP is an essential first step to establishing the foundations for developing AI and machine learning (ML) approaches for medical image analysis in histopathology. In this section we explore the opportunities and implementation challenges surrounding DP. We then briefly explore the considerations to harnessing histopathology and radiology data for AI approaches.

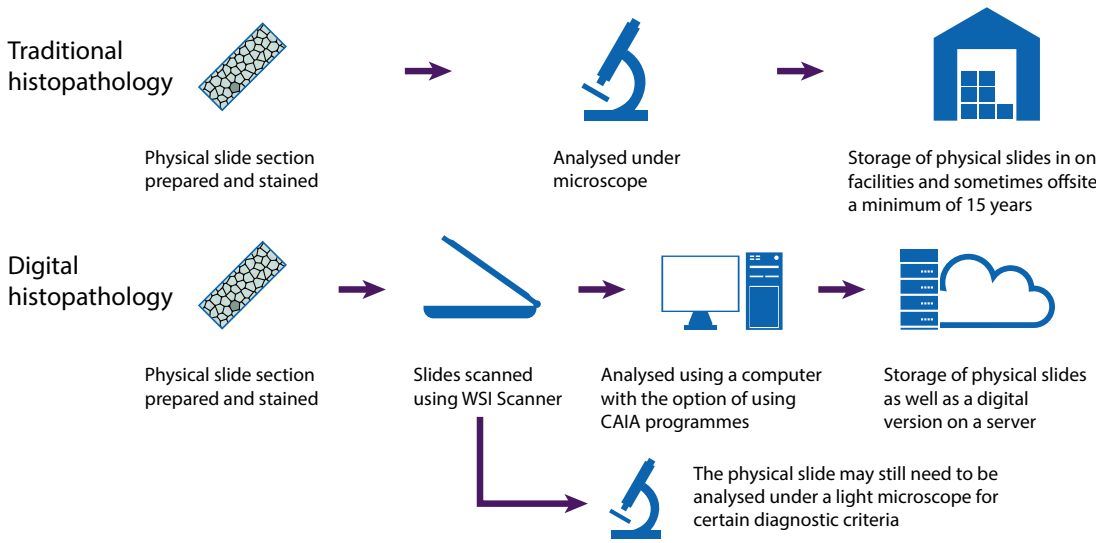
Box 5.1 Definitions

- **Artificial intelligence** is the development and use of computing systems concerned with making machines work in an intelligent way
- **Machine learning** is a form of artificial intelligence that uses algorithms which iteratively learn from data rather than being explicitly programmed. Performance tends to improve with experience and more datasets
- **Digital pathology** the digitisation of the entire pathology workflow including Whole Slide Imaging, image analysis and electronically barcoding specimens
- **Computer aided diagnostics or detection** are algorithms that assist with the interpretation of medical images. These can be based on conventional programming or ML algorithms

Digitisation of the histopathology workflow

Traditionally, histopathology specimen analysis is carried out by a histopathologist using a light microscope to examine a sample on a glass slide. More recently, the ability to capture pathology slides digitally has been possible due to the development of whole slide imaging (WSI) scanners which can capture an image of the magnified whole slide and allow for the image to be stored, viewed and analysed on a computer (Figure 4).

Figure 4. Steps involved in traditional and digital histopathology workflows



In addition to WSI scanners, DP workflows include electronic labelling, storage and analysis of digital images. A particular area of interest for DP is to enhance histopathology image analysis. Histopathology involves the sectioning of a tissue sample – usually a biopsy of a suspected cancerous lesion – to assess changes and characteristics that may be indicative of disease.

Tissue sections are stained to highlight structures such as cell membranes and nuclei but can also be stained by immunohistochemistry (IHC) to identify particular proteins present that may indicate disease.

Why digitise histopathology?

For cancer diagnosis, the analysis of a histopathology specimen requires expert second opinion and a multidisciplinary team meeting. This means that the physical slides must be sent to different pathologists, and in many cases, different hospitals, and since only one person can examine the slide at a time this results in a high administrative burden and delayed diagnoses.

Although published studies for some diagnostic applications have found current DP technology to have limitations for cytology, and in identifying subtle nuclear changes and microorganisms [241]. The digitisation of slides has several benefits for histopathology, including:

- Enabling experts to access slides simultaneously and in different locations
- Allowing pathologists to work remotely without the physical slide
- Digital images can be backed up and multiple copies can be saved
- Whilst stains and tissue on physical slides can degrade over time or if they are not stored correctly, a digital image will keep its integrity indefinitely
- Enhancing training and teaching for new and existing pathologists

Based on the result of histopathology specimen analysis, pathologists can stratify patients for treatment options based on the quantity, intensity, morphology and presence of markers in a tissue sample. Many studies have looked at ways to assist and automate these often laborious and time consuming tasks with computer aided image analysis (CAIA) programmes. Currently, these can perform very specific tasks in a highly prescribed way.

For example, there are some FDA approved CAIA programmes for quantifying cells presenting with an IHC stain associated with HER2/neu and ER/PR (oestrogen/progesterone receptor) markers in breast cancer samples. These markers dictate what treatment the patient can receive so are valuable for ensuring that the patient is prescribed the correct treatment for their type of cancer.

Currently these CAIA programmes are strictly for assistive purposes and the final diagnosis is made by the pathologist. Evidence is emerging that these algorithms may result in better reproducibility [242] and quicker turnaround time to diagnosis [243].

Currently, clinically applied CAIA approaches are based on conventional programming and not on AI or ML. However, results from CAIA based on AI and ML have been promising for breast[128, 244] and prostate [245] cancer in particular, where tumour grading and biomarker scoring is important for determining treatment stratification and disease prognosis. Histopathology analyses for these cancers have particularly marked inter-observer variation [245, 246] and will therefore likely benefit from automated processes.

The first key step to applying these potentially valuable approaches is digitisation – to have the slide in a format amenable to applying ML. The second but simultaneous step that needs to occur is the standardisation of image production and data collection so that quality datasets can be collated.

The current state of implementation of digital pathology

Policy developments

The Life Sciences Industrial Strategy [145] highlights digitalisation and AI to transform pathology and imaging as part of the proposed Health Advanced Research Programme. In response to this report, the Life Sciences Sector Deal [238] details collaborations between a number of companies and the UK's academic institutions, charities and the NHS, to drive growth in the sector.

Philips, Roche Diagnostics and Leica are three major companies in discussion with the government and the NHS to develop a trail-blazing digital pathology programme using AI [238]. Philips is currently working with three NHS Sites in Scotland to determine how a networked digital pathology services can improve patient outcomes in remote areas [247].

NHS implementation

The implementation of DP workflows has been recommended by Cancer Research UK (CRUK) [248] and individual clinicians [239, 240] for histopathology image analysis. The Royal College of Pathologists responded to the CRUK recommendations positively, however, initial guidance highlights that there are still some areas of pathology that will require traditional methods (e.g. ability to recognise microorganisms) [249]. There are various WSI systems that are CE-marked for use in primary diagnostics such as, Philips' IntelliSite Pathology Solution and Leica's Aperio AT2 slide scanner. Whilst some laboratories are leading the way in the NHS, there is no widespread adoption of WSI scanners and DP workflows in routine practice.

Most engagement with this technology has tended to be within University teaching hospitals, for example, Leeds Teaching Hospitals, The University of Warwick and University Hospitals Coventry and Warwickshire, Bradford Teaching hospitals, University College London hospitals, Birmingham Heartlands Hospital and Greater Manchester Trusts.

Some groups of hospitals have formed pathology networks amongst themselves to facilitate learning and sharing of images; The East and South Yorkshire pathology EASYPath network exists between Sheffield, Hull and East Yorkshire Hospitals.

Research development

In 2015 CRUK awarded five centres – Queen's University Belfast, the University of Southampton, University College London, University of Manchester, University of Newcastle and University of Leicester – collaborative five-year Network Accelerator Awards. The aim of this research collaboration is to establish a national digital pathology and image analysis platform for solid tumours in CRUK centres, drive adoption of DP for cancer research, establish technology standards and grow the Centres' reputation and leadership in this field.

While these research initiatives, trials in the NHS, and guidance from professional bodies are useful for strengthening the evidence base, a system-wide approach working with the relevant professional bodies is needed to ensure widespread adoption of digital pathology. This would be best achieved by a national commissioning approach rather than commissioning via individual departments. Support is needed to cover the initial start-up costs – procuring WSI scanners and IT infrastructure – but also the upkeep of such services.

Key consideration: To support the implementation of digital pathology, and its subsequent delivery within the health system, the NHS should consider a system-wide approach, in consultation with relevant professional bodies such as the Royal College of Pathologists.

International healthcare implementation

The DP infrastructure is more prevalent in some nations including Sweden [250] and Canada [251] where the patient population is diffuse and pathologists may be concentrated in discrete centres [240]. The uptake of DP workflows in the United States has been slow and fragmented, however, in 2017, the FDA cleared Philips IntelliSite Pathology Solution for primary diagnostics which is the first (and currently, only) WSI system to be FDA approved. It is expected that this will lead to an increased uptake of DP in the United States.

Digitisation of pathology workflows is an important step for not only realising the benefits of DP (Chapter 4) but also the potential of AI and ML approaches to image analysis. This second aspiration can only be achieved when consistent, high-quality and robust DP infrastructure is in place. Furthermore, it will be vital to ensure the files can be effectively harnessed for AI and ML approaches which pose a number of implementation considerations.

System implementation challenges and considerations for action

Validation of equipment and evidence collection on effectiveness

One of the major barriers to widespread implementation is the apparent lack of large, high quality validation studies for each WSI scanner and each application. Although there are many validation studies in the literature comparing the concordance between diagnoses made by analysing samples on glass and those on digital images [240], they vary in quality – factors such as sample selection could bias results – and many are of small size, suggesting that more studies are required [252].

The Health Technology Assessment programme and the Digital Pathology Association (DPA) have recently released guidelines for the design and execution of validation and verification studies for all aspects of DP, including image analysis [253]. Furthermore, the Royal College of Pathologists (RCPath) published a diagnostic DP strategy in 2017, which states that laboratories must ensure that the technology has been through these validation and verification processes. The strategy also states that the consensus is that diagnostic work carried out by digital microscopy is not inferior to conventional microscopy [241].

Demonstrating the benefits of digital images over physical slides with robust evidence (on performance, efficiency improvement, and cost) is essential to engage pathologists, laboratory staff and budget holders. CAIA approaches are likely to improve efficiencies when adopted at scale, which can only be achieved by widespread adoption of DP.

Key consideration: The health system should consider how to support validation studies in digital pathology, utilising guidelines from HTA and DPA, and with support from RCPath. These studies could collect information on increased efficiency and cost-savings of DP, information which could be used to engage users about the benefits of this technology.

Key consideration: A universal standard for how WSI systems are calibrated will help to avoid inconsistencies between scanners and between different sites using the same type of scanner. One approach is for manufacturers to ensure that image viewing and analysis software can be calibrated so that outputs are consistent between different scanners (e.g. depth and shades of colours).

Pathology workflow and IT infrastructure issues

The implementation of digital pathology introduces an additional step in the workflow for pathologists and laboratory staff as the physical slide needs to be scanned using the WSI-scanner before it can be analysed digitally.

Key consideration: The transition to digital pathology will alter the workflow and will therefore need to be supported by training for laboratory staff and pathologists in digital image analysis including navigating digital images on a computer as opposed to a microscope. Consideration needs to be given as to how this step can be integrated into workflows.

The transfer to digital also brings challenges in terms of file storage and processing power required to manage these images. Unlike radiology images, histopathology analysis takes place at a subcellular level meaning that the quality and magnification of digital images needs to be very high. Commercial vendors are creating scanners and software that create large, high resolution files, to enable detailed analysis and ensure high granularity of images is available for when new CAIA approaches are ready. DP images are typically 10X the size of radiology images and therefore, consume a substantial amount of digital space. In addition to this, there are typically multiple slides from each tissue sample and more than one tissue sample from each patient (e.g. up to 12 for prostate samples).

The processing power to navigate these image files may be beyond the capability of many local NHS IT infrastructure systems. Dedicated IT systems are required to process and store images; this could be local hardware solutions or cloud-based services or a combination of both.

An advantage of cloud-based systems is that the overhead of updating, maintaining and securing the IT platform is overseen by the cloud provider (Chapter 4) and they are useful for instant access to a virtual network for pathology laboratories to share images with each other.

Key consideration: The NHS should consider the informatics infrastructure requirement for the clinical deployment of DP, for example hardware or cloud-based solutions to store image files.

Key consideration: A national strategy is required to standardise all aspects of DP including; slide preparation, image capturing, file format and resolution, and supplementary information. The creation of a nationwide repository for collating histopathology images and diagnoses based on these standards will be invaluable for the training of AI and ML CAIA approaches, noted in the Life Science strategy as one of four Health Advanced Research Programmes [238].

The interoperability of WSI software from different providers is essential to ensure that the health system can benefit from being able to share images digitally. Furthermore, there needs to be seamless communication between WSI systems and other current data storage platforms such as the Picture Archiving and Communication System (PACS), currently used by radiology, the Laboratory Information Management System and EHRs.

Key consideration: It will be important for organisations such as the RCPath and DPA to continue to work with suppliers to ensure their platforms interface with other hospital systems used by healthcare professionals, to ensure interoperability of systems and that there are no technological barriers to image sharing and analysis throughout the whole health system.

Advanced image analysis

In addition to histopathology, radiology is another area promising area for the application of ML approaches especially as radiology is already predominantly digitised. For example, CAIA integration into pre-existing PACS for radiology images has been achieved in some centres in the United States [254, 255].

Key considerations for developing ML-enabled CAIA approaches in both radiology and histopathology include:

- Multi-centre data collection: to develop machine learning software that can recognise a broad range of pathology, large datasets of medical images are required to train the algorithms. Whilst these datasets are archived within individual hospitals, data collected across centres (ideally across the country) would prove the most valuable for ML-training. This is not only because the performance of the algorithm tends to improve with more training data, but also because each institution and individual radiologist or pathologist may use slightly different protocols for image production and different equipment to capture the images. Therefore, training datasets need to account for this inherent variability otherwise there is the risk the algorithms performance may vary depending on the source of the data.
- Standards and harmonisation: in addition to standards to reduce the inherent variability in datasets collected across centres, standards and harmonisation of processes for data collection, labelling, and preparation for ML-training and application are required to reduce the potential for bias in how the algorithms operate.
- Validating AI programmes and generating evidence on the performance of ML algorithms: currently there are few multicentre trials to validate ML CAIA. Clinical adoption will require standards for the validation of algorithms and evidence on the performance of machine learning software, and a clear articulation of the benefits. The Royal College of Radiologists are working to establish a framework for AI including quality assurance.
- Understanding the legal and regulatory environment regarding the use of AI and ML algorithms in clinical decision making. The regulatory landscape surrounding the use of algorithms and processing of personal data is evolving. The implications of the General Data Protection Regulation, and the In Vitro Diagnostic Regulation and the Medical Device Regulation on the development and use of machine learning algorithms will need to be understood especially as the 'black-box' nature of some ML algorithms – i.e. it is not always identifiable how the algorithm comes to a decision outcome – could make them difficult to regulate. More broadly the regulatory framework for AI in healthcare will need to be explored.

Conclusions

The digitisation of pathology images is the vital first step that must be taken to harness the potential for advanced image analysis using AI and ML approaches. By enabling a system-wide uptake of DP workflows, the benefits of DP itself will be realised and the use of image analysis software can begin to aid pathologists in making diagnoses. In addition to image digitisation, a national strategy for collating medical image data is essential for the future development and application of ML technologies.

5.7 3D printing

Three-dimensional printed (3DP) objects facilitate the personalisation of medicine through the development of anatomical models for surgical planning and/or the customisation of devices and implants for individual patients.

The most common 3DP objects are anatomical models for pre-operative planning or surgical references. Whilst there are substantially fewer studies on customised implants, evidence is rapidly gaining for certain procedures. 3D printing of personalised prosthetics and orthotics holds promise, however currently the main areas under development are models, guides and implants therefore this section will focus on these areas.

Surgical planning

3D printed anatomical models for planning surgery have been shown to improve perioperative care by reducing operative time [87, 88, 256–258], intraoperative blood loss [87], and postoperative complications and recovery time [87, 256]. 3D models are particularly helpful for assessing intricate and complex anatomical structures and abnormalities, for example in neurology, cardiology, craniomaxillofacial surgery and in the treatment of spinal deformities.

Models can also be used to reduce implant surgery time by allowing the surgeon to pre-mould an implant to the patient's unique anatomy [259] or be used as a reference during the operation [260]. Importantly, pre-operative planning is enhanced when using 3DP models rather than 3D rendered images [261] or generic, commercially available models [262].

3D printed surgical guides or templates have been found to improve navigation and surgery of the mandible, teeth, shoulder, spine, hip or knee. Studies have found that using these guides or templates decreases operating times, blood loss, inflammatory response, and improves tactile sensation in the treated area and/or aesthetics [263].

3D printed anatomical models have also been found to be useful for medical student learning [264–267]. Furthermore, clinicians can use anatomical models to improve clinician and patient communication [268]. This could help with informed consent [269] and ease anxiety.

3D printed implants

Personalised 3DP implants have been used across a variety of surgical specialties, including craniomaxillofacial [90, 91, 270], thoracic [92], spinal [93], and orthopaedic [94, 96] surgery. Personalised implants and orthotics can be created by reverse engineering the object to fit an individual's anatomy as opposed to off the shelve one size fits all devices.

Generally, customised implants reduce surgery time and improve patient outcomes by:

- Reductions in recovery times
- Reductions in the number of operative procedures and returns to clinic
- Better aesthetic results for maxillofacial surgery [90, 91]

Personalised implants have also been used as preventative measures for anticipated side effects of therapy. For example, titanium implants for tumour bearing bone have been found to be effective at eliminating the risk of fractures, implant failures and loosening after undergoing microwave ablation treatment for bone tumours around the knee [95].

Case study 1: Hospital implementation of a 3DP service

Addenbrooke's hospital in Cambridge established a 3D printing service within their Trust with funding from the Addenbrooke's Charitable Trust and the Alborada Trust [88]. The hub is based in a centralised department of the hospital – the Media Studio – to allow access to all clinicians from every specialism, as well as to external projects. The Trust has invested in a dedicated technician to run all aspects of the service as often clinicians do not have the time or expertise to prepare a radiology images for 3D printing. The proximity of the service enables clinicians to work with the technical staff to ensure the images are segmented and the appropriate structures are printed. One challenge to the uptake of this service is that some end-users have found it more difficult to gain reimbursement for 3D models where they are not currently part of routine practice.

Case study 2: Commercial 3DP hub implementation

3D LifePrints (3DLP) is a commercial provider of 3D printing services based in the Innovation Hub at Alder Hey Children's hospital in Liverpool. It services 20 NHS hospitals (including Alder Hey, Liverpool Chest and Heart Hospital and the Royal Liverpool Hospital), private hospitals and Universities. Clinicians work with the experts at 3DLP to create 3D rendered images from MRI and CT scans, which are used to print anatomical models. Cardiologists at Liverpool Heart and Chest Hospital secured external funding for patient communication models for individuals with congenital heart disease, and for 3DP models for pre-surgical planning for patients with atrial septal defects.

Implementation of 3D printing in the NHS

Whilst the use of 3D printing applications in dentistry, the production of hearing aids and personalised insoles is widespread [271], adoption of the technology for personalised implants, pre-surgical anatomical models is localised to specific centres with access to the technology and relevant expertise.

A number of hospitals in England have 3D printers onsite however there is wide variation in the extent of their use and in the existence of dedicated staff to run the 3D printing service. Some hospitals have in-house commercial entities to provide 3D printing services that can be accessed by all departments and other hospital clinicians, for example 3D LifePrints (3DLP) at Alder Hey Children's Hospital (see Case study 2). Those who do not have access to, or are not aware of onsite facilities, may use national and international commercial providers such as Belgium-based company, Materialise.

3D printed models and implants

3D printing is currently the most commonly used fabrication technique for anatomical models, predominantly used for pre-surgical planning [259]. In addition to their use in craniomaxillofacial, cardiothoracic and orthopaedic surgery, there have frequent 'one-off' uses in other specialities involving complex procedures. For example, a 3D model was used as a surgical reference during an operation in a young child with a complex congenital spinal deformity [272]. There are various clinical trials underway for the use of 3D printed anatomical models in liver tumour [54], cerebral aneurysm [273], hepatobiliary and pancreatic [274], and heart [275] surgery.

In the NHS, personalised implants are most commonly used for craniomaxillofacial reconstruction. The Centre for Applied Reconstructive Technologies in Surgery, in Wales, has been one of the leading innovators in using 3D printing technology for such reconstructive surgery and prosthetics. Several clinical trials are underway for 3D printed jaw implants [276], airway implants [277], ankle bone [278] and bone defect [279] restoration.

Implementation of 3D printing in other healthcare systems

A proposal for NHS Scotland has set out plans for a National 3D printing framework project [280]. The plan includes centralised hubs of 3D printers run by the NHS in Scotland, which all hospitals will have access to.

Other health systems and nations are incorporating and developing policy for 3DP personalised medical devices:

- Personalised knee implants are covered by the German Public Healthcare system fund
- Japan's Central Social Insurance Medical Council cover 3DP anatomical models for pre-surgical planning under the standard medical insurance payment range in 2016
- Australia's private health funds cover patient specific instrumentation for knee replacement. The Australian government are running a consultation on regulatory changes related to personalised and 3DP medical devices [281]
- In the US, a number of healthcare organisations and academic hospitals, (including the Mayo Clinic [282], and Cleveland Clinic) have established in-house 3D printing centres
- The FDA have reviewed more than 100 3DP manufactured devices and in December 2017 the FDA issued new guidance to advice device manufacturers on technical aspects of 3D printing [283]. The agency is also working to establish a regulatory framework for the application of existing laws and regulations that govern device manufacturing to non-traditional manufacturers – like facilities that create 3DP personalised devices for patients [284]

The reimbursement methods for 3DP objects in other health systems are not clear. In some instances, costs for a particular patient pathway are not itemised and are bundled together, therefore payers would not be aware if they are dealing with a 3DP or standard manufactured device [285].

System implementation challenges for 3D printing

There are promising results in the literature pertaining to use of 3DP for implants [91–93, 270, 279] and surgical planning [257, 261] but there remain various challenges to overcome to facilitate widespread implementation and use.

Support for implementation of services

There is currently significant activity within the health system for using 3DP objects. While 3D printing is a multi-use technology with wide-ranging applications across different departments, its use tends to be localised, and confined to specific clinical departments or individual clinicians with knowledge of the technology.

Key consideration: The health system should consider the development of clear commissioning guidelines to support the implementation of those applications with good clinical utility evidence.

Service establishment and access

There are substantial costs involved in setting up 3D printing services within NHS departments. These include procuring 3D printers, developing appropriate IT infrastructure and fully training staff in use of this technology.

At the same time 3D printing technology is evolving and improving and a challenge is to enable access whilst avoiding overinvestment in technology that may be supplanted by better solutions in a few years. This could be done best by delivering services via regional hubs owned by the NHS or through commercial providers, embedded in hospitals.

Consideration should be given to:

- The number of requests that are likely in a given hospital/Trust to generate sufficient income to cover the full running costs of the service including the investment of 3D printers, materials and dedicated technical staff
- Ability to provide services to external customers (i.e. Universities, private healthcare)
- Where the service is located. In-house 3D printing services may benefit from being centralised to encourage use by all departments both within and outside of the Trust

As described above, many hospitals already have 3D printers but not all departments have access to this technology or are aware of its existence. Making these services available to all would open up the opportunities and appetite for use, however engagement efforts are required to increase awareness.

Key consideration: The health system should consider an NHS-wide strategy for the implementation, delivery and access of 3D printing services, which takes into account service providers, service demand and location.

Key consideration: Ensuring 3D printing services are accessible by all departments, for example though centralised location and by facilitating access to existing 3D printers in hospital departments, could help to improve access to and promote the use of printers.

Payment for 3D printed objects

A key barrier to widespread use is the difficulties in obtaining funding for 3DP objects. There are two principal reasons for this. Firstly, 3DP models and implants are particularly useful for treating complex and often rarer disorders and therefore there are fewer large scale, long term trials being carried out. This makes assessing the benefits of one-off requests difficult. Secondly, even for those operations where there is good evidence of improved medical outcomes, such as models for complex hip replacement [86], it can be difficult to obtain reimbursement as cost savings may not be directly applicable to the department who is funding the object.

For example, the increased cost of producing a 3D object may be paid for out of a budget that does not cover surgery and post-surgery where the savings may be seen. When considering evidence as to the efficacy of 3D printing, the whole patient pathway should be assessed. For example, the cost of the pre-operative planning might be more expensive but the patient could spend fewer days in hospital post-operatively or have fewer readmissions. Currently, surgical models and guides are funded either through case by case request from departmental budgets or by research grants – with no standardised funding route.

Key consideration: The health system should consider how it assesses evidence in support of the use of 3D printing to treat rare conditions. Cost-benefit analyses should be carried out for each type of 3D printing application and surgery type covering the whole patient experience including collecting information on long-term patient outcomes.

Sufficient IT infrastructure

The process of printing models from medical images can be time intensive. The processing and segmentation of 3D images, reverse engineering implants, guides and prostheses with CAD to fit an individual's anatomy requires interdisciplinary knowledge. There have been cases where the surgery has commenced before a 3DP object has been available [88].

Furthermore, this process requires expertise in computer science and in-depth knowledge of anatomy. A recent review noted that 10 minutes saved in the operating room could potentially be equivalent in cost to one hour of work spent producing a 3DP object [286].

Key consideration: Appropriate IT infrastructure is needed to support the sharing of image files between NHS departments, Trusts and potentially outside of the NHS, to commercial providers to speed up request completion. Consideration should be given as to how product quality control processes are established and how clinicians can interact with 3D printing technicians to ensure product quality.

Evidence and guidance

A challenge with collating a substantial evidence base for 3D printing is that many accounts are for one-off case reports or have very small sample sizes (e.g. fewer than 10 in the intervention group). This is particularly apparent for 3DP implants for less common conditions, for example, slipped capital femoral epiphysis [257]. Furthermore, there is a lack of long term, follow-up studies for personalised implants compared to standard procedures.

For each application and type of surgery/therapy, there needs to be a process for collecting evidence to demonstrate whether 3D printing personalised objects improves patient outcomes and reduces costs compared to standard procedures, especially when the initial outlay of expenses will increase.

Key consideration: Guidance from professional bodies (e.g. Royal College of Surgeons and Royal College of Radiologists) on how to carry out clinical utility and validity studies is required to improve reporting of experiences using 3DP for specific surgeries, including evidence of benefits obtained due to 3D printing.

Key consideration: It is likely that most of these devices will fall under the Health Institution Exemption in the Medical Device Regulation. Briefly, this exemption applies if the device is not produced on an industrial scale, remains within the same legal entity and has no market equivalent. 3D printing services will need to comply with the Regulation upon scaling up their operations; however, scaling up production of bespoke objects raises many unresolved regulatory issues. It will therefore be necessary to review the regulatory landscape surrounding 3D printing as the use of bespoke objects continues to increase, particularly to ensure the long-term safety of these devices.

Conclusion

3D printed objects have been found to be useful for various disciplines and applications. Currently they are most commonly employed for craniomaxillofacial surgery. Evidence of clinical utility is emerging in cardiology, neurology and orthopaedics [86]. Published studies indicate that 3DP objects can in principle improve patient outcomes and reduce operation times, however, long term follow-up studies for 3DP implants and cost-benefit analyses are lacking. 3D printing is a multi-use technology, but currently implementation is fragmented. An NHS-wide strategy to support implementation of 3D printing is required to fully realise the benefits of this technology across the whole of the health system.

5.8 Pharmacogenomics

Pharmacogenomics (PGx) is defined as 'the study of variation of DNA and RNA characteristics as related to drug response' [287]. DNA and RNA may act as determinants of response to drugs by affecting their absorption, distribution, metabolism and excretion (pharmacokinetics), and by modifying their effects on cell receptors and downstream biochemical pathways (pharmacodynamics). Pharmacogenomic information has the potential to strengthen personalisation of medicine by enabling selection of targeted therapies, avoidance of drugs which may contribute to serious adverse drug reactions (ADRs), and informing more precise drug dosing for patients based upon their individual genetic make-up.

Selection of targeted therapies

Analysis of germline, somatic and pathogen genomes can provide more precise information on the causative mechanism of diseases or refine a clinical diagnosis. This can aid targeting of therapies to optimise treatment. For example, gain-of-function mutations in the *PCSK9* gene are a known underlying cause in some cases of familial hypercholesterolaemia (FH), for which *PCSK9* inhibitors are now in clinical use [288, 289]. *BRAF*^{V600} genetic mutations are present in approximately 50% of cases of metastatic malignant melanoma, and can be targeted using *BRAF* inhibitors to increase overall and progression-free survival of those affected [290, 291]. Analysis of pathogen genomes such as *Mycobacterium tuberculosis* can aid more precise targeting of antimicrobials (Section 5.3).

Reduction of serious adverse drug reactions

The association between the *HLA-B*5701* allele and hypersensitivity to the HIV antiretroviral drug abacavir, first described more than a decade ago, was the first genetically determined drug response used to inform therapy selection in routine clinical practice. Carriers of *HLA-B*5701* have a significantly increased risk of severe and potentially fatal hypersensitivity reactions to abacavir [292, 293]. Numerous gene-drug pairs have been associated with severe ADRs, including 30 human leucocyte antigen (HLA) alleles to-date. The *HLA-B* allele, *HLA-B*1502*, is strongly associated with severe cutaneous hypersensitivity reactions to the antiepileptic drug carbamazepine in patients from South East Asian countries [294]. For other alleles, such as *HLA-B*58:01* (allopurinol) and *HLA-A*31:01* (carbamazepine), evidence from clinical studies supports the use of pre-emptive screening for decreasing the incidence of cutaneous ADRs in Taiwanese and Japanese patients, respectively [295, 296].

More precise drug dosing

More recently, it has been demonstrated that testing the genetic variants in two genes, *CYP2C9* and *VKORC1* to determine dosing of the anticoagulant warfarin is superior to standard dosing strategies of this drug [297]. This strategy achieves and maintains optimal anti-clotting activity more quickly, including reducing the incidence of excessive anti-clotting activity which can lead to internal or external bleeding or bruising.

In a randomised controlled trial (RCT), no clinically significant bleeding or clotting events were recorded in the group of patients receiving genotype-guided warfarin dosing, although the RCT was not large enough to yield statistically significant differences between the two patient groups [297]. Anticoagulation levels which fall above the target range for those on treatment are associated with double the incidence of major bleeding events [298]. The ability to optimise anticoagulant treatment is important because of the very high numbers of patients involved (e.g. there are more than 1.3 million people in the UK with atrial fibrillation, many of whom will be on anticoagulant medication to prevent stroke), meaning that these drugs, including warfarin, are among the drugs responsible for the highest number of ADRs and fatal ADRs reported in inpatients [299].

Pharmacogenetic information indicative of poor metabolism may also inform the avoidance of certain drugs altogether, such as certain *CYP2C19* variants which render the antiplatelet drug clopidogrel significantly less effective for preventing adverse cardiovascular and cerebrovascular events in high-risk patients [300, 301].

Policy importance

PGx has been identified as one of the key applications within personalised medicine in the NHS England policy document *Improving Outcomes through Personalised Medicine* [7], and highlighted as an opportunity to deliver precision medicine in the annual report of the Chief Medical Officer in 2016 [3].

The state of implementation in healthcare systems

Current use of PGx in the NHS

The use of PGx in the NHS is limited at present, and testing for very few pharmacogenes is available to clinicians. Some genes of relevance to drug responses are included as integral parts of disease-specific gene panels provided by NHS laboratories, but access to these panels for the purposes of pharmacogenetic testing is highly unlikely to be permitted unless also clinically indicated for diagnostics.

Selection of targeted therapies

The selection of targeted molecular therapies is the most advanced and well-circumscribed application of PGx, and is dependent in almost all cases upon companion diagnostic testing to provide precision molecular diagnoses (Chapter 3 and Section 5.3) and to determine patient suitability for treatment. The majority of drugs for which companion diagnostic testing is required are used in oncology, and are accompanied by clinical guidelines devised by NICE, for example *EGFR* mutation testing in patients with NSCLC [150]. Examples of targeted non-cancer therapies licenced for use include ivacaftor for cystic fibrosis and *PCSK9* inhibitors for FH.

Reduction of serious adverse drug reactions

Although numerous gene-drug pairs have been associated with severe ADRs, pre-treatment genetic screening is only mandated in British prescribing guidelines prior to commencing abacavir and carbamazepine therapy. UK and international drug guidelines specify that pre-treatment screening for *HLA-B*5701* should be performed for abacavir [302–304] and that testing for *HLA-B*1502* should be performed in individuals of Han Chinese or Thai descent prior to initiating carbamazepine [302, 304].

There are other drugs for which pre-treatment screening is advocated in prescribing guidelines and carried out using phenotypic methods, such as the immunosuppressant drug azathioprine and chemotherapy agent mercaptopurine which are metabolised by thiopurine s-methyltransferase (TPMT). UK pharmaceutical guidelines recommend that TPMT activity is assessed using phenotypic tests of red blood cells before prescribing these drugs, which is currently performed at three centres in the UK (M. Pirmohamed, personal communication). It has not been established whether genetic *TPMT* testing offers significant clinical advantages over phenotypic tests, but there is a very high level of agreement between genetic and phenotypic tests, and genetic testing may be beneficial for patients who have recently received a blood transfusion or drugs that affect TPMT activity, such as aspirin [305, 306].

More precise drug dosing

Among the drugs for which PGx may inform dosing strategies, the strongest evidence base is for genotype-guided dosing of warfarin, which has been determined to be a cost effective intervention and is currently being integrated into clinical practice at pilot sites in the UK [307, 308]. Testing for genes involved in the metabolism of chemotherapy drugs is also being implemented at some cancer centres within NHS hospitals. Dihydropyrimidine dehydrogenase (DPYD) gene variants are implicated in toxicity arising from the chemotherapy drugs 5-fluorouracil and capecitabine [309].

Nationwide *DPYD* testing is currently only available as part of an unrelated NHS congenital cataract and lens malformation gene panel, but a programme has been developed at the Royal Bournemouth Hospital that provides *DPYD* testing to all patients with colorectal cancer planned to receive fluropyrimidine based chemotherapy to inform initial dosing and improve safety. Currently, this scheme is independently funded by a local charity grant (B. Eccles, personal communication). The cost-effectiveness of *DPYD* testing at Southampton General Hospital is under investigation (E. Copson, personal communication).

Together, these examples indicate increasing clinical demand for PGx testing to inform drug selection and dosing, but demonstrate that testing is only available in a limited number of NHS centres and for a limited number of applications.

Current use of PGx in international healthcare systems

No nationwide pre-emptive PGx testing programmes (i.e. testing for variants in genes that may impact future prescribing) are currently in place in any healthcare system. Although some access to PGx testing is available in many countries worldwide, this is fragmented and largely based upon local policies or proximity to hospitals where clinical research is conducted [310, 311].

Based on the currently limited availability of PGx testing, therapeutic recommendations formulated by the Dutch Pharmacogenetics Working Group (DPWG) have been incorporated into all electronic prescribing and medication surveillance systems in the Netherlands, and those generated by the Clinical Pharmacogenetics Implementation Consortium (CPIC) are included in US clinical practice guidelines and recommendations [312].

Direct-to-Consumer tests are also available, of which a minority are eligible for funding by health insurance providers [310, 313]. Reimbursement of PGx testing is considered to be one of the most significant barriers to wider implementation, and is hindered by the lack of definitive evidence of clinical benefit and cost effectiveness for many available tests [310].

Evidence gaps and barriers to implementation

Although there has been a great deal of research and activity by leaders in the PGx research community, there has been only modest progress in implementation into healthcare services. This has been due to the following barriers:

Clinical utility

The lack of evidence of the clinical utility of PGx testing is affecting its implementation. A number of initiatives led by research consortia are underway to assess the clinical value of PGx testing in order to support its implementation into routine healthcare.

The Ubiquitous Pharmacogenomics (U-PGx) consortium is leading the **Pre**emptive **P**harmacogenomic testing for prevention of **A**dverse drug **Re**actions (PREPARE) randomised cross-over trial, involving 8000 patients across seven European countries (Table 5.7). A pre-emptive pharmacogenetic testing programme is also in place at St. Jude Children's Research Hospital in the US, which is dually strengthening the evidence base for gene-drug associations and evaluating the effectiveness of incorporating PGx data in electronic health records (EHRs) of almost 4,000 paediatric patients [314].

Whilst these studies will help to clarify which pharmacogenes should be included in PGx testing, it has yet to be determined which patient groups would maximally benefit from testing, at what stage testing should be implemented, and whether testing should be offered on a pre-emptive or reactive basis.

Guidelines for practice

Approximately 150 drugs approved by the EMA and the FDA contain PGx information in their drug labels [315, 316]. Dosing recommendations for some pharmacogene variants associated with commonly prescribed drugs, including those for pain relief, cardiovascular disease, anticoagulation, diabetes, mental health disorders and cancer, have been developed by CPIC and DPWG.

These guidelines share a good level of agreement for most gene-drug pairs [317], and are collated and published by the Pharmacogenomics Knowledge Base (PharmGKB) as a freely accessible online resource [43]. PGx testing is required or recommended in PharmGKB guidelines for up to 40% of FDA- and EMA-approved drugs with associated PGx information, of which the majority are drugs used in oncology that require companion diagnostic tests for targeted therapy [315]. Development of clinically validated guidelines is awaited for drugs where PGx testing is not currently mandated.

Supporting the clinical workforce

A significant obstacle to implementing PGx testing in healthcare settings is ensuring awareness among the clinical workforce of the availability of and rationale for testing. Addressing this will rely upon improved education throughout training, and simplifying access to testing and interpretation of PGx data as part of routine clinical practice. As well as conducting basic research, a number of international consortia are involved in promoting implementation by evaluating the utility of pre-emptive genotyping and strategising the incorporation of PGx data into EHRs and clinical pathways [318]. These include the US-based Implementing Genomics In practice (IGNITE) network, and the European Pharmacogenetics Implementation Consortium (Eu-PIC) (Table 5.7).

Barriers to implementation and considerations to support the integration of pharmacogenomics into the patient pathway in the UK

It can be anticipated that pharmacogenomics testing will become increasingly important within patient pathways in the next few years. It is therefore important that this is approached strategically and that plans are developed that will ensure:

- The capacity and capability of the laboratory services
- The development of the clinical workforce to incorporate testing effectively and safely into their clinical practice
- The development of clinical guidelines that will support good evidence-based practice
- The development of infrastructure to support changes in clinical pathways
- Consideration of ethical, legal and social aspects, particularly where issues have special relevance for PGx testing

Table 5.7: International PGx networks, consortia and collaborations

Organisation	Activities
Ubiquitous Pharmacogenomics (U-PGx)	Collaboration of experts across 16 different organisations in 10 European countries. Leading the PREPARE study, which will assess the clinical value of pre-emptive testing of thirteen important pharmacogenes (*CYP2D6*, *CYP2C9*, *CYP2C19*, *CYP1A2*, *CYP2B6*, *CYP3A5*, *SLCO1B1*, *TPMT*, *DPYD*, *VKORC1*, *UGT1A1*, *HLA-B* and *CYP3A4*) [319], with the potential to guide the dose and drug selection of over 40 commonly prescribed medications, including some of those most involved in ADRs and fatal ADRs [299]. It is anticipated that PGx testing will particularly benefit older patients for whom simultaneous use of multiple medications (polypharmacy) is common.
Clinical Pharmacogenetics Implementation Consortium (CPIC)	Aims to improve the translation of PGx genetic data into clinically actionable results by publishing peer-reviewed gene-drug clinical practice guidelines. CPIC guidelines [320] are available on guidelines.gov, and referenced in PubMed, ClinGen and PharmGKB databases [44].
Royal Dutch Association for the Advancement of Pharmacy Pharmacogenetics Working Group (DPWG) [321]	Multidisciplinary working group that includes clinical pharmacists, physicians, clinical pharmacologists, clinical chemists, epidemiologists, and toxicologists. DPWG develop PGx-based prescribing recommendations and integrate these into electronic prescribing and medication surveillance systems [317].
Implementing Genomics In practice (IGNITE) network	Comprises six genomic medicine research sites tasked with finding ways to incorporate genomic information into EHRs and clinical decision support tools [322].
European Pharmacogenetics Implementation Consortium (Eu-PIC) [323]	Aims to improve patient care in Europe by integrating PGx data into clinical care and facilitating PGx-guided personalisation of drug therapy [323].
Electronic Medical Records and Genomics (eMERGE) network	US-based network which works to combine DNA biorepositories with EHR systems in support of implementing genomic medicine. The eMERGE-PGx project is a collaboration with the Pharmacogenomics Research Network in which the process and clinical outcomes of integrating PGx data into EHRs and clinical decision support tools is being evaluated [324].

Capacity and scope of the National Genomic Laboratory Services

Implementation of PGx will be directly impacted by the National Genomic Medicine Service capacity to accommodate PGx testing, data interpretation and reporting (Chapter 2). Work is currently ongoing to assess whether PGx testing could be included in the 2019/20 National Genomic Test Directory (Chapter 2).

Capacity of National Genomic Medicine Service to provide pharmacogenetic data will depend on a number of strategic decisions regarding eligibility for and scope of PGx testing including:

- Which patient groups will be eligible for testing and at what point in the patient pathway PGx data should be obtained
- Whether testing will occur pre-emptively or as part of drug-specific pre-treatment screening

Other implementation considerations around how PGx testing should be undertaken include:

- Which pharmacogene variants are of greatest clinical value
- Which testing modalities could be used, e.g. defined pharmacogene panels, WGS or tests on an individual gene basis. There is increasing interest in point-of-care testing that may be able to yield PGx data at the time of prescribing, although no such devices have yet received regulatory approval for use in clinical settings [325]
- The format of PGx result reporting, and how to ensure its inclusion in clinical decision-making. Increasing the number of PGx tests and requirements for PGx data analysis and reporting will increase the workload of clinical scientists, but is not expected to require significant input from clinical geneticists. Results from the PREPARE study and other clinical trials should allow progress to be made in these areas.

Key consideration: NHS England should estimate the required capacity and distribution for PGx testing and ensure that this is incorporated into the new National Genomic Medicine Service configuration.

Key consideration: NHS England should consider provision for the continued assessment of evidence regarding in which patient groups and when in the patient pathway PGx testing is most beneficial to patient care, and which pharmacogenes and testing modalities are most appropriate to improve clinical outcomes.

Key consideration: Consideration should be given to who will be responsible for interpreting and reporting PGx data to healthcare professionals in patient facing roles, and the format in which this information can be most effectively conveyed to ensure its inclusion in clinical decision-making processes.

Access to testing and development of clinical education

It seems likely that PGx testing may well be undertaken in diverse clinical pathways by clinicians with little or no formal education in genomics. It is vital that those currently in practice are equipped through training support to manage their patients effectively and safely, taking advantage of these new opportunities.

Specifically they will need to:

- Become competent to identify patients who would benefit from testing, discuss the testing and obtain consent
- Refer for testing and liaise with the laboratory to choose the most appropriate test
- Understand the clinical implications of the results and be able to discuss these with their patient to make appropriate clinical decisions.

Health Education England have established a Genomics Education Programme which provides educational resources and optional courses to NHS staff and the multi-professional workforce that will be involved in the delivery of genomic medicine.

Key consideration: A designated programme of education for relevant qualified healthcare professionals and particularly doctors can help to ensure that they are competent to use PGx testing appropriately for their patients. Ideally this would be incorporated into the curricula of those in training at all levels.

Key consideration: Consideration should be given to which professionals can offer PGx testing, including the possibility that pharmacists and clinical pharmacologists may be involved.

Key consideration: Consideration should be given to how testing services should provide support to healthcare professionals offering PGx testing.

Supporting uptake through changes to care pathways and health systems

Beyond education of the clinical workforce, it will be important to address how PGx data can be promptly accessed in clinical settings, and how this data can be used to inform drug selection and/or dosing strategies alongside other important considerations such as co-morbidities, contraindications and patient characteristics (e.g.: age and body mass index).

A key strategic decision remains regarding whether existing therapeutic guidelines, such as those devised by PharmGKB, will be adopted by the NHS to inform therapeutic decisions. Inclusion of PGx data in clinical decision-making will depend upon absolute clarity of such prescribing guidance.

Universal adoption of EHRs and electronic prescribing systems, improvement of data storage infrastructure and development of clinical decision support tools would greatly improve accessibility and utility of PGx data in clinical settings.

Incorporating PGx data into institutional clinical decision support systems has been shown to improve prescribing patterns aimed at reducing patient risk, and to significantly reduce emergency department visits and hospital readmissions in older patient requiring numerous concurrent medications [47, 326].

An alternative strategy is for patients to carry their own PGx information in the form of a safety-code card that can be scanned to retrieve PGx-based dosing recommendations, as is being trialled in the PREPARE study.

Key consideration: NHS England should consider how the supporting digital infrastructure could support the equitable provision of PGx testing and ensure that these are built into the developing systems.

Key consideration: As PGx testing services are established through the National Genomic Medicine Service, NHS England should consider developing processes to collect evidence of the impact on clinical decision making as this could serve to encourage broader adoption of PGx testing in the future.

Ethical, legal and economic considerations

Ethical and legal considerations for PGx are largely shared with those for genomic medicine, which are reviewed elsewhere [327, 328]. Salient points to note for PGx testing include the following:

- There is potential for incidental findings (secondary findings) as part of PGx testing for pharmacogene variants with known disease associations, such as *UGT1A1* in Crigler-Najjar syndrome and Gilbert syndrome, and others with no currently known disease associations
- As far as possible, evidence for clinical effectiveness should be derived from populations that cover the full range of ethnicities. Otherwise there should be awareness of inequities and the potential for discrimination in the service offer
- The availability of PGx data may also create legal and regulatory pressure to incorporate this information into clinical trials, to protect participants from ADRs and to strengthen clinical research outcomes. Whilst this could be beneficial for patients, it will be important to recognise the complexities this raises
- ADRs cost the NHS approximately one billion pounds annually, and could be prevented by pre-emptive PGx testing in an estimated 20-30% of cases [42]. Economic evaluations of PGx-guided treatment are largely favourable and considered to be cost-effective or cost-saving in most analyses conducted [329]
- With continued improvements in precision diagnosis and development of targeted therapies, it will be important that companion diagnostic assays for targeted therapies are simultaneously developed and regulated to enable prompt incorporation of targeted therapies into clinical pathways

Key consideration: Understanding the ethical, legal and regulatory perspective on PGx testing can help to support developing services.

Conclusions

PGx testing is technically viable and testing for variants/genes with established clinical validity is feasible and currently being incorporated into the provision of genetic testing within the reconfigured NHS laboratory system. The challenge will be to roll out and extend this from the limited set of tests that are currently well evidenced and implemented (at least in some places) into a way of supporting therapeutics across a much wider range of applications. This will require a concerted effort to ensure that the best evidence emerging from international research and practice is incorporated into UK guidelines for the management of a wide group of patients.

The use of these guidelines will only be possible through the development of capable clinicians and appropriate clinical, laboratory and digital infrastructure.

5.9 Policy considerations

The technologies described in this chapter all have the potential to have significant impact on the delivery of personalised care in the NHS over the next three years and beyond. While considerations specific to each technology have been made, areas have been identified where action is required that are common to many or all technologies.

- **NHS-wide strategy to support implementation:** Top-down support for the implementation of new technologies is required, involving the relevant professional bodies where necessary to develop the appropriate guidance, commissioning advice and guidance, and clarity on funding pathways.
- **Standards:** Across each technology, for the datasets generated to provide consistent and reliable insights, standards for data generation, storage, capture, analytics, and interoperability are essential. Similarly, harmonisation of laboratory methodologies, and care delivery, is important to ensure consistent delivery of clinical services across the population.
- **Technology development:** The health system will need to consider whether test/technology development and delivery can be done in-house or outsourced and which approach is the most cost-effective in the long term. This involves weighing up any short term establishment costs against longer term cost savings. There are relative advantages and disadvantages of each approach in terms of the cost, amount of risk taken on, and flexibility in responding to health system needs. For each technology the degree of centralisation of resources and expertise needs to be considered.
- **IT infrastructure:** Personalised medicine requires cutting-edge IT infrastructure to collect, store, manage and analyse patient data, including up-to-date software and hardware, interoperability of file formats and interconnectivity enabling data sharing within the health system. Implementing this infrastructure will require significant resources including financial.
- **Data sharing and integration:** Pooling and integrating data across the health system (e.g. medical images) is needed in order to improve and develop many personalised medicine approaches. A strategy for collating data including clarity around the regulations surrounding the use of patient data, (how it can be shared, with whom and under which circumstances, and the necessary safeguards involved) can facilitate appropriate data sharing. A common understanding of the legitimacy of data sharing across all Trusts is key to harmonising data sharing practice.
- **Raising awareness of personalised medicine approaches:** Different specialities across the health system need to be aware of the relevance and applicability of the approaches to their clinical practice and for their patients. This includes information about new technologies on the medical curriculum, raising awareness of these technologies with current health professionals and providing the relevant training. Engagement regarding the benefits of new technologies, including how they might change working practice and the impact on patient outcomes is required. Mechanisms are needed to share expertise within the health system, particularly to collect, share and incorporate feedback about how technologies are working in patient care pathways.

- **Ongoing assessment:** This includes service evaluations, EQA, accreditation, assessment of gaps in current provision, and incorporation of feedback from evaluation/EQA and from current service users to improve provision.
- **Managing small patient numbers in different disease areas:** With improved tools for stratification and personalisation, patients with common diseases, such as some cancers, are being categorised into ever smaller groups, in effect meeting the criteria for a rare disease in terms of numbers. The health system needs to consider how it approaches management of small groups of patients and what kind of support is available for small-scale trials to investigate the effectiveness of therapies, down to n of 1 studies.
- **Co-approval of treatments/approaches and the technologies needed to prescribe them:** There is a need for a coordinated approach in terms of the approval of interventions and any associated technologies that are needed in order to prescribe them appropriately. Examples include companion diagnostic tests needed to prescribe targeted therapies and tests required to enable pharmacogenomics decisions.

Achieving the vision

Each of the technologies reviewed in this report can support the aspiration to move away from a one size fits all approach to more personalised healthcare focused on prevention, earlier disease detection, and targeted interventions. However, positive transformational change depends on short-term targets set against a backdrop of longitudinal planning to embed personalised medicine into mainstream healthcare.

The previous chapters have focused on the near-term opportunities to realise the benefits of personalised medicine and associated challenges.

This chapter takes a more visionary perspective to consider how, in the longer term, technologies and knowledge could enable a whole system transformation towards personalised medicine as the norm.

6.1 Building on current foundations

The preceding chapters describe the growing array of technologies and innovations available to personalise medicine. These range from approaches that could increase personalisation through improvements in information capture and the utilisation of existing data – e.g. family history and health records – to complex and emerging technologies that either generate or process large volumes of clinically useful information e.g. artificial intelligence and 'omics approaches.

In principle, each of the technologies reviewed in this report and other novel innovations that may surface in the future, can support the aspiration to move away from a one size fits all approach to more personalised healthcare focused on prevention, earlier disease detection, and targeted interventions.

In practice, positive transformational change will rely on short-term targets set against a backdrop of longitudinal planning to embed personalised medicine into mainstream healthcare. The new era of genomic testing (Chapter 2), concurrent with the other near-term opportunities to realise the benefits of personalised medicine described in this report (Chapter 5) are core to driving the momentum towards longer-term system transformation.

Demonstrating the impact on patient outcomes and the health service, but also sharing experience and learning from the challenges associated with implementation and adoption of these near-term approaches could serve to stimulate an environment receptive to the wider adoption of personalised medicine.

6.2 Moving towards whole system transformation

Ongoing innovation – driven in significant part through cross-discipline collaboration – is widening the options available for prevention, diagnosis and treatment. Across the landscape of healthcare technologies there is an increasing convergence and coalescence of biomedical, digital, and computer science and engineering systems. For example:

- **Machine learning** is expected to play an important role in medical image processing; artificial intelligence holds great promise for the analysis of large datasets generated by 'omics and digital technologies
- **Stem cell therapies** are being combined with gene editing techniques for targeted therapies
- **Regenerative medicine** in concert with 3D printing could offer tailored solutions for the repair of damaged or disease tissues
- **Bioengineering technologies** may radically change capabilities for remote physiological monitoring
- **Genomics and other 'omics** will interface with a range of specialisms to inform diagnostics and therapeutics.

This intersection of different technologies to deliver personalised medicine is a trend that will continue.

Implemented as discrete, individual approaches these technologies are unlikely to have the desired impact on health. Instead the success of the implementation and utilisation of these approaches will rely on synergistic and coordinated integration into healthcare. More broadly the transformative potential of personalised medicine will be contingent on the ability to incorporate the new approaches as mainstream and integral features rather than adjunct components of the health system. This will require an overarching and collaborative strategy and dissolving of silos between different healthcare sectors to consider how traditional specialisms can interact to take a 'whole person' approach to healthcare. If harnessed effectively the data amassing from biomedical and digital technologies can provide better context to an individual's health, and the effective flow of this patient information can enable greater coordination across the health system – and in turn – greater personalisation of care.

The future for personalised medicine in healthcare

As the health system contends with increasing prevalence of patients with multiple chronic medical conditions (multi-morbidity) and an ageing population, it is clear that change is needed. In addition to improving care for patients with existing conditions, the ambition of NHS England in harnessing the potential of personalised medicine is to drive a shift towards prevention and ultimately 'a health system focused on improving health not just treating illness' [7].

Among the features of a personalised health approach that may drive this transformation and a radical upgrade in prevention, are:

- A culture shift in how the health system interacts with patients, collates, manages, and analyses their data
- Increasing data collection potentially throughout the life cycle – truly cradle to grave
- Better understanding of population diversity – with greater awareness of what is normal for an individual and therefore clearer indication of when an intervention might be required
- Greater citizen engagement – access to health records; interaction with citizen collected data

Personalised medicine - the impact

The impact of personalised medicine will be felt most by patients and the health system, however there will also be a wider impact on innovation and the economy as a whole.

The benefits to patients of offering more personalised medicine approaches will be:

- Greater opportunity to prevent disease
- More precise diagnosis and prognosis
- More targeted treatments and interventions – that are more likely to be effective, and fewer patients given interventions that will not benefit them
- Safer treatments – lower risk of adverse effects
- Unnecessary or unexpected hospital stays, or other interactions with the health system, are minimised

In turn, the benefits for the health system will be:

- More efficient and effective use of health system resources
- Greater awareness of benefits throughout the system – e.g. how investment in one area could result in greater savings elsewhere in the patient pathway
- More streamlined care delivery supported through digitisation and appropriate data sharing to improve patient care
- Greater engagement and empowerment of citizens and patients to manage and maintain health

Crucially important risks that need to be mitigated against include:

- Inequitable access potentially resulting in worsening health inequalities
- Inappropriate use of valuable and limited health resources on interventions lacking sufficient evidence of clinical utility
- Unrealistic expectations or misunderstandings of the clinical impact of the personalised approaches
- Increased potential for liability arising from risks associated with more complex interventions

By committing to the delivery of personalised medicine, a culture of innovation will permeate healthcare and ensure that new technologies are integrated optimally and swiftly for the benefit of patients. This culture can be supported by the aims of the Accelerated Access Review, the Life Sciences Industrial Strategy, and other relevant innovative initiatives including the Cell and Gene Therapy Catapult and Genomics England.

A more connected and digital health system can create a virtuous cycle whereby data generated during the course of healthcare can inform research and development efforts to further improve and inform personalised medicine technologies and approaches. Consequently, demand for personalised healthcare can encourage processes to innovate, design, manufacture and deliver care and treatment with an impact on UK PLC and the wider economy. For example:

- The Industrial strategy will provide support for basic science research and translational research: it is estimated that every pound invested in medical research delivers an average return of 25p every year thereafter [330]
- Manufacturing initiatives will boost the UK's ability to stay at the forefront of complex medical manufacturing e.g. the Cell and Gene Therapy catapult manufacturing centre and support for manufacturing recommended by the Industrial Strategy
- The data and knowledge generated from personalised medicine approaches could stimulate the development of new treatments

More broadly the emphasis on prevention may facilitate greater economic productivity, fewer sick days, and less long-term sickness.

6.3 Achieving the wider vision of personalised medicine

In the near term, the programmes and technologies outlined this report can help to deliver personalised medicine approaches. However, in order to drive systemic change this delivery will need to occur in the context of a long-term strategy focused on developing a foundation of supportive technologies and strategies that are vital to delivering personalised medicine in the health system. While the focus of this evidence synthesis is to review the technology landscape, clearly pressing social, ethical, economical questions abound and must also be addressed in concert. Similarly, although we focus here on the delivery of personalised medicine by the health system, the necessary changes can only be fully realised by working with partners and stakeholders.

This will entail:

- **Contribution of information technology and data science sector:** Is essential to create the unique electronic tools and systems to capture, manage, analyse and secure patient data. In addition to the computational hardware and software, the vast volumes of data generated by biomedical and digital technologies can only be harnessed by a cadre of human skills in data science, ranging from bioinformaticians, 'omics analysts, data curators, and AI expertise. The health system will require a strategy on how to acquire and/or access these skills sets.
- **Engagement within and beyond the health system:** The broader impetus for personalised medicine can only be achieved through engagement with health professionals to develop and implement new technologies in the NHS and to inform the wider workforce on what they can do, and to empower them to change practice. Equally, public engagement is vital given the necessity of patient and citizen data in improving and developing personalised medicine.
- **Building networks and partnerships:** The innovation required to advance personalised medicine will require the health system to work in partnership with industry, enterprise, and academia. A number of government-level initiatives that consider healthcare in the broader context will contribute to fostering these partnerships and the short- and longer-term delivery of personalised medicine. The recommendations of the Accelerated Access Review, which focus on support for the development of new technologies and quicker access to them, supported by digital innovations, will start to be enacted in 2018. In the medium term, a concerted effort to enact the recommendations of the Life Sciences Industrial Strategy will support the delivery of new technologies in the next 5–10 years through reinforcement of the UK research base, delivery of clinical trials, and support for manufacturing.

Collaboration between the different organisations involved in these initiatives and engagement with key stakeholders including the healthcare workforce and the public is vital to ensure that the integration of personalised medicine is effective for all of those who will be affected by its implementation and delivery.

Conclusions

Personalised medicine holds enormous potential to transform healthcare, improve patient outcomes and provide a radical shift towards prevention. Overcoming technological challenges are just one element in striving to fully embed personalised medicine into mainstream healthcare. Social, ethical, legal and economic considerations will require careful consideration.

Furthermore, personalised medicine will entail a new and arguably more collaborative approach of working with innovators, academia, industry, and crucially with patients and the publics.

If achieved, personalised medicine will not only offer high-quality, efficient care with improved clinical outcomes and population health, but also the foundations to create a truly learning health system that collates evidence from clinical encounters, to inform ongoing improvement and innovation in healthcare practice.

Appendices

Appendix 1: Key considerations for NHS England

Personalised medicine holds enormous potential to transform healthcare in England and improve patient outcomes. Key to maintaining momentum towards greater personalisation in the long term are the near term opportunities set out in this report. The benefits for patients and the health system, including more precise diagnosis and prognosis, more targeted and personalised interventions, better understanding and prediction of individual disease risk, could together support more efficient and effective use of health system resources. These elements will be essential for delivering on the ambitions of the Five Year Forward View.

Each technology presents its own specific challenges, but with the increasing convergence of these technologies, successful utilisation will depend on a synergistic and coordinated approach to implementation. As the single biggest integrated healthcare system in the world the NHS is uniquely poised to achieve this.

Underpinning and enabling technologies to support healthcare infrastructure

Key consideration	Section	Topic
Digitisation of health data is the cornerstone of many personalised medicine applications. A continued drive towards the implementation of interoperable EHRs, with standardised data capture, is essential to realising the near-term and future benefits of personalised medicine.	4.2	Establishing the critical healthcare infrastructure: healthcare digitisation
In order to respond to rapidly evolving data needs for personalised medicine, it is essential the informatics and computing systems that are established are robust, interoperable and scalable to meet increasing demand.	4.2	Establishing the critical healthcare infrastructure: computing infrastructure
Secure safeguarded systems to protect data are central to fostering patient trust for the data sharing which is essential to conducting the high-quality research to drive personalised medicine.	4.2	Establishing the critical healthcare infrastructure: digital security, trust and patient preference
The development of novel personalised medicine applications will take place in the context of patient preferences for data sharing. Future planning for personalised medicine should consider the implications of the national data opt-out on the availability of health data for medical research and clinical services.	4.2	Establishing the critical healthcare infrastructure: digital security, trust and patient preference

Technologies for personalised disease monitoring

Key consideration	Section	Topic
Whilst the value of risk assessment tools and family history data for personalised medicine is recognised – especially within genetics, their potential within secondary and primary care has yet to be unlocked. Beyond genetics, the development and incorporation of these tools can be supported by defining the contexts for when to use and clear mechanisms for how to use, including the types of information capture required and standards for interoperability with existing digital systems.	4.3	EHR dependent technologies: risk assessment and family history tools
The effective utilisation of POCT devices could be supported by an assessment of the clinical contexts within which POCT is likely to have the greatest impact on patient outcomes and an assessment of how care pathways may need to adapt to maximise the utility of these devices	4.4	Personalised disease monitoring: point of care devices
The health system will need to assess whether and how to engage with the growing consumer-driven digital health movement.	4.4	Personalised disease monitoring: m-health and digital wearables
The health system should seek to develop policy on whether and how to fully harness the benefits of consumer driven 'citizen generated' health data	4.6	Internet of things: remaining agile in a fast developing digital world
The underpinning informatics hardware and software solutions being established across the health system should be sufficiently agile and flexible to respond to the rapidly evolving capabilities of digital health technologies	4.6	Internet of things: remaining agile in a fast developing digital world

Circulating tumour DNA testing for therapy selection in cancer (technologies for greater molecular characterisation)

Key consideration	Section	Topic
To support NHS implementation clinical guidelines on the use of ctDNA testing in NSCLC should be considered. These could be developed by one or more of the professional societies and organisations, such as: British Thoracic Oncology Group, British Thoracic Society, Royal College of Pathologists, Cancer Research UK (including the ECMC network), NICE (clinical guidelines for lung cancer). Clinician and laboratory expertise in ctDNA testing should be actively collected to inform these guidelines.	5.2	Circulating tumour DNA testing for therapy selection in cancer: guidelines
Ongoing service evaluation is required to ensure that the health system has the appropriate information for informing further implementation.	5.2	Circulating tumour DNA testing for therapy selection in cancer: technology development - what is the best test?
Engagement about ctDNA testing can take place within the multidisciplinary team (MDT) – ideally via an individual who can act as a point of contact for queries and information. This person could be a clinician, clinical scientist or a pathologist.	5.2	Circulating tumour DNA testing for therapy selection in cancer: engagement within the health system
The use of laboratory websites to include up-to-date and clear electronic referral information and resources, including testing information, costs and logistics should be considered.	5.2	Circulating tumour DNA testing for therapy selection in cancer: service logistics
Healthcare commissioners should formally consider the provision of ctDNA services in lung cancer, including whether *EGFR* ctDNA tests should be included on the National Genomic Test Directory, and improve and strengthen current service provision.	5.2	Circulating tumour DNA testing for therapy selection in cancer: health system challenges and initiatives

Circulating tumour DNA testing for therapy selection in cancer (technologies for greater molecular characterisation)

Key consideration	Section	Topic
Future service development efforts should consider how the results from current service evaluations and External Quality Assessment, key lessons learned and expertise in ctDNA testing in NSCLC could be captured and incorporated to inform future uses and delivery of other ctDNA tests by the health system.	5.2	Circulating tumour DNA testing for therapy selection in cancer: health system challenges and initiatives
The health system should assess how the establishment of ctDNA testing services and their validation could be supported by the promotion of available funding, promotion of test funding structures, linking of test development into accelerated access of technologies and support of collaborative test development.	5.2	Circulating tumour DNA testing for therapy selection in cancer: health system challenges and initiatives
NHS England should consider how patients can have improved access to funded targeted therapies and take steps through policy development to ensure that the health system is better prepared to implement targeted therapies when commissioned.	5.2	Circulating tumour DNA testing for therapy selection in cancer: health system challenges and initiatives

Regenerative medicine (technologies for personalised therapeutic interventions)

Key consideration	Section	Topic
Routine use of RM will require the recommendations made by the Regenerative Medicine Expert Group and the House of Commons Science and Technology committee enquiry on regenerative medicine to be fully addressed. Progress towards these recommendations would benefit from a national coordinated approach, with designated leadership who are appropriately equipped to harmonise and drive forward efforts for advancing RM in the UK.	5.4	Regenerative medicine: stem cell and gene therapies - challenges affecting uptake and implementation

Regenerative medicine (technologies for personalised therapeutic interventions)

Key consideration	Section	Topic
The health system should consider new models of evidence gathering in support of therapies for rare conditions with low patient numbers, right down to 'n of 1' therapies. The volume and type of evidence required should be considered in light of the cost / benefit of the therapy, number of patients who benefit and how often evidence should be reassessed as patients undergo long-term follow up.	5.4	Regenerative medicine: stem cell and gene therapies - building and considering the evidence base
The health system should consider new models of reimbursement that support end-stage therapy development and testing through clinical trials as a way of balancing costs and risks for both manufacturer and the health system, while ensuring there is minimal delay in patients benefitting from proven innovative therapies.	5.4	Regenerative medicine: stem cell and gene therapies - support for therapy development and reimbursement strategies
Clear regulatory processes are required if the UK is to effectively adopt beneficial RM treatments, including clear regulatory definitions of different treatments. The RASRM 'one-stop shop' is an example of how a coordinated regulatory approach can be realised – this approach should be assessed to determine if it is meeting the current needs of the RM landscape. Other regulatory constructs such as specials exemption or OMP status should be reviewed to determine if and how they can best respond to developments in RM and encourage inward investment in RM in the UK.	5.4	Regenerative medicine: stem cell and gene therapies - regulation
Manufacturing infrastructure should be flexible and able to respond to the emergence of new technologies and demand for products, ensuring that there is not a delay in research into RM or in the delivery of RM therapies to the health system.	5.4	Regenerative medicine: stem cell and gene therapies - manufacture of RM
The health system should consider how to take advantage of current infrastructure and expertise to deliver some RM therapies, and how to support and strengthen these centres.	5.4	Regenerative medicine: stem cell and gene therapies - health system delivery of RM

Regenerative medicine (technologies for personalised therapeutic interventions)

Key consideration	Section	Topic
The health system should seek to ensure the development and/or maintenance of an appropriate skill base, in addition to ensuring that physicians are adequately trained to understand, adopt and apply RM. Surgical and medical expertise are required that complement emerging RM therapies in different clinical specialities.	5.4	Regenerative medicine: stem cell and gene therapies - health system delivery of RM
Given the logistical challenges associated with live cell and tissue treatments, the geographic distribution of centres of excellence in RM should be considered in order to achieve equitable access, with consideration of specific population concerns, e.g. sickle cell treatments in areas where population demographics result in greater demand. The establishment of three new ATTCs across the country will help to make RM more accessible, provided appropriate expertise can be built-upon at these locations [209]	5.4	Regenerative medicine: stem cell and gene therapies - health system delivery of RM

Transcriptomics (technologies for greater molecular characterisation)

Key consideration	Section	Topic
The results from ongoing clinical trials should be considered if/when evidence emerges in support of the use of GEP tests. The cautious and considered utilisation of early access schemes (such as PONDx in France) may help in terms of gathering evidence on clinical effectiveness. The aforementioned new draft guidelines from NICE state that test data collected from the future use of any recommended GEP in breast cancer prognosis and treatment stratification must be submitted to the National Cancer Registration and Analysis Service for further assessment of test data and its link to chemotherapy use, recurrence risk and survival outcomes [219]. This will be beneficial to the further scrutiny of the tests.	5.5	Transcriptomics: collection and assessment of appropriate evidence

Transcriptomics (technologies for greater molecular characterisation)

Key consideration	Section	Topic
Due to the large numbers of tests being developed, the healthcare system should consider a flexible approach to panel adoption and how to allow for timely review of updated evidence on current tests and evidence in support of new tests, to determine which tests should be adopted. As foundational knowledge of the transcriptome grows, the combination of genes included within panels should evolve and recommendations for individual panel use will change over time.	5.5	Transcriptomics: collection and assessment of appropriate evidence
The health system should consider regular review of advances in transcriptomics technologies and the optimal approach for delivering testing via the Genomic Laboratory Hubs, either in-house or via commercial providers.	5.5	Transcriptomics: commercial development of GEP tests
The NHS could consider whether to seek agreements with manufacturers whereby one or more parts of the analysis are internalised to the laboratory ordering the test.	5.5	Transcriptomics: impact on patients of using GEP tests
The health system should consider how to manage the different sample requirements of RNA-based tests in a timely manner, and how it might make best use of the pathways established to collect fresh tissue (as part of 100,000 Genomes Project) for clinical specialities where collecting this sample type is not standard practice.	5.5	Transcriptomics: impact on patients of using GEP tests

Advanced image analysis (Underpinning and enabling technologies)

Key consideration	Section	Topic
To support the implementation of digital pathology, and its subsequent delivery within the health system, the NHS should consider a system-wide approach, in consultation with relevant professional bodies such as the Royal College of Pathologists.	5.6	Advanced image analysis: Digital pathology, research development

Advanced image analysis (Underpinning and enabling technologies)

Key consideration	Section	Topic
The health system should consider how to support validation studies in digital pathology, utilising guidelines from HTA and DPA, and with support from RCPath. These studies could collect information on increased efficiency and cost-savings of DP, information which could be used to engage users about the benefits of this technology.	5.6	Advanced image analysis: validation of equipment and evidence collection on effectiveness
A universal standard for how WSI systems are calibrated will help to avoid inconsistencies between scanners and between different sites using the same type of scanner. One approach is for manufacturers to ensure that image viewing and analysis software can be calibrated so that outputs are consistent between different scanners (e.g. depth and shades of colours).	5.6	Advanced image analysis: validation of equipment and evidence collection on effectiveness
The transition to digital pathology will alter the workflow and will therefore need to be supported by training for laboratory staff and pathologists in digital image analysis including navigating digital images on a computer as opposed to a microscope. Consideration needs to be given as to how this step can be integrated into workflows.	5.6	Advanced image analysis: pathology workflow and IT infrastructural issues
The NHS should consider the informatics infrastructure requirement for the clinical deployment of DP, for example hardware or cloud-based solutions to store image files.	5.6	Advanced image analysis: pathology workflow and IT infrastructural issues
A national strategy is required to standardise all aspects of DP including; slide preparation, image capturing, file format and resolution, and supplementary information. The creation of a nationwide repository for collating histopathology images and diagnoses based on these standards will be invaluable for the training of AI and ML CAIA approaches, noted in the Life Science strategy as one of four Health Advanced Research Programmes [238].	5.6	Advanced image analysis: pathology workflow and IT infrastructural issues

Advanced image analysis (Underpinning and enabling technologies)

Key consideration	Section	Topic
It will be important for organisations such as the RCPath and DPA to continue to work with suppliers to ensure their platforms interface with other hospital systems used by healthcare professionals, to ensure interoperability of systems and that there are no technological barriers to image sharing and analysis throughout the whole health system.	5.6	Advanced image analysis: pathology workflow and IT infrastructural issues

3D printing (technologies for personalised therapeutic interventions)

Key consideration	Section	Topic
The health system should consider the development of clear commissioning guidelines to support the implementation of those applications with good clinical utility evidence.	5.7	3D printing: support for implementation of services
The health system should consider an NHS-wide strategy for the implementation, delivery and access of 3D printing services, which takes into account service providers, service demand and location.	5.7	3D printing: service establishment and access
Ensuring 3D printing services are accessible by all departments, for example though centralised location and by facilitating access to existing 3D printers in hospital departments, could help to improve access to and promote the use of printers.	5.7	3D printing: service establishment and access
The health system should consider how it assesses evidence in support of the use of 3DP printing to treat rare conditions. Cost-benefit analyses should be carried out for each type of 3D printing application and surgery type covering the whole patient experience including collecting information on long-term patient outcomes.	5.7	3D printing: payment for 3D printed objects
Appropriate IT infrastructure is needed to support the sharing of image files between NHS departments, Trusts and potentially outside of the NHS, to commercial providers to speed up request completion. Consideration should be given as to how product quality control processes are established and how clinicians can interact with 3DP technicians to ensure product quality.	5.7	3D printing: sufficient IT infrastructure

3D printing (technologies for personalised therapeutic interventions)

Key consideration	Section	Topic
Guidance from professional bodies (e.g. Royal College of Surgeons and Royal College of Radiologists) on how to carry out clinical utility and validity studies is required to improve reporting of experiences using 3DP for specific surgeries, including evidence of benefits obtained due to 3DP.	5.7	3D printing: evidence and guidance
It is likely that most of these devices will fall under the Health Institution Exemption in the Medical Device Regulation. Briefly, this exemption applies if the device is not produced on an industrial scale, remains within the same legal entity and has no market equivalent. 3D printing services will need to comply with the Regulation upon scaling up their operations; however, scaling up production of bespoke objects raises many unresolved regulatory issues. It will therefore be necessary to review the regulatory landscape surrounding 3D printing as the use of bespoke objects continues to increase, particularly to ensure the long-term safety of these devices.	5.7	3D printing: evidence and guidance

Pharmacogenomics (technologies for greater molecular level characterisation)

Key consideration	Section	Topic
NHS England should estimate the required capacity and distribution for PGx testing and ensure that this is incorporated into the new National Genomic Medicine Service configuration.	5.8	Pharmacogenomics: capacity of the National Genomic Laboratory Service
NHS England should consider provision for the continued assessment of evidence regarding in which patient groups and when in the patient pathway PGx testing is most beneficial to patient care, and which pharmacogenes and testing modalities are most appropriate to improve clinical outcomes.	5.8	Pharmacogenomics: capacity of the National Genomic Laboratory Service
Consideration should be given to who will be responsible for interpreting and reporting PGx data to healthcare professionals in patient facing roles, and the format in which this information can be most effectively conveyed to ensure its inclusion in clinical decision-making processes.	5.8	Pharmacogenomics: capacity of the National Genomic Laboratory Service

Pharmacogenomics (technologies for greater molecular level characterisation)

Key consideration	Section	Topic
A designated programme of education for relevant qualified healthcare professionals and particularly doctors can help to ensure that they are competent to use PGx testing appropriately for their patients. Ideally this would be incorporated into the curricula of those in training at all levels.	5.8	Pharmacogenomics: access to testing and development of clinical education
Consideration should be given to which professionals can offer PGx testing, including the possibility that pharmacists and clinical pharmacologists may be involved.	5.8	Pharmacogenomics: access to testing and development of clinical education
Consideration should be given to how testing services should provide support to healthcare professionals offering PGx testing.	5.8	Pharmacogenomics: access to testing and development of clinical education
NHS England should consider how the supporting digital infrastructure could support the equitable provision of PGx testing and ensure that these are built into the developing systems.	5.8	Pharmacogenomics: supporting uptake through changes to care pathways and health systems
As PGx testing services are established through the National Genomic Medicine Service, NHS England should consider developing processes to collect evidence of the impact on clinical decision making as this could serve to encourage broader adoption of PGx testing in the future.	5.8	Pharmacogenomics: supporting uptake through changes to care pathways and health systems
Understanding the ethical, legal and regulatory perspective on PGx testing can help to support developing services.	5.8	Pharmacogenomics: ELSI

Appendix 2: Acknowledgements

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Appendix 3: Abbreviations

3DP	Three-dimensional printing
3DLP	3D LifePrints
ACI	Autologous chondrocyte implantation
ADA-SCID	Adenosine deaminase specific severe combined immunodeficiency disorder
ADR	Adverse drug reaction
AI	Artificial intelligence
ALL	Acute lymphoblastic leukaemia
AMR	Antimicrobial resistance
ASGES	Age/sex/gene expression score
ATMP	Advanced therapeutic medicinal product
BRAF	*B-Raf* proto-oncogene, serine/threonine kinase
CAD	Computer aided design
CAIA	Computer aided image analysis
CAR-T	Chimeric antigen receptor T-cells
CCG	Clinical Commissioning Group
CDS	Clinical decision support
CE	Conformité Européenne
CGH	Comparative genomic hybridization
CGTC	Cell and Gene Therapy Catapult
CPIC	Clinical Pharmacogenetics Implementation Consortium
CQC	Care Quality Commission
CRISPR	Clustered regularly interspaced short palindromic repeats
CRUK	Cancer Research UK
CT	Computerised tomography
ctDNA	Circulating tumour deoxyribonucleic acid
CUP	Cancer of unknown primary
DLBCL	Diffuse large B-cell lymphoma

DNA	Deoxyribonucleic acid
DP	Digital pathology
DPA	Digital Pathology Association
DPWG	Dutch Pharmacogenetics Working Group
DPYD	Dihydropyrimidine dehydrogenase
ECMC	Experimental Cancer Medicine Centres
EGFR	Epidermal growth factor receptor
EHR	Electronic health records
EMA	European Medicines Agency
eMERGE	Electronic Medical Records and Genomics
EQA	External Quality Assessment
ER	Oestrogen receptor
FDA	US Food and Drugs Administration
FFPE	Formalin-fixed paraffin-embedded
FH	Familial hypercholesterolemia
FMT	Faecal microbiota transplantation
FYFV	Five Year Forward View
GEP	Gene expression profiling
GLH	Genomic Laboratory Hub
HER	Human epidermal growth factor receptor
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
HSCT	Haematopoietic stem cell transplantation
HTA	Human Tissue Authority
IHC	Immunohistochemistry
IOMT	Internet of Medical Things
IOT	Internet of Things
IVD	*In vitro* diagnostic device
KRAS	*KRAS* proto-oncogene, GTPase
MHRA	Medicines and Healthcare products Regulatory Agency

MIB	Medtech innovation briefing
ML	Machine learning
MRC	Medical Research Council
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MRSA	Methicillin resistant *Staphylococcus aureus*
MS	Mass spectrometry
NDG	National Data Guardian
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIPD	Non-invasive prenatal diagnosis
NIPT	Non-invasive prenatal testing
NMRS	National Mycobacterial Reference Service
NSCLC	Non-small cell lung cancer
OMP	Orphan medicinal product
PACS	Picture archiving and communication system
PCR	Polymerase chain reaction
PDB	Portable diagnostics bioassay
PGD	Pre-implantation genetic diagnosis
PGx	Pharmacogenomics
PharmGKB	Pharmacogenomics Knowledge Base
PHE	Public Health England
POCT	Point of care testing
PR	Progesterone receptor
PREPARE	Pre-emptive Pharmacogenomic testing for prevention of Adverse drug Reactions trial
RASRM	Regulatory Advice Service for regenerative medicine
RCPath	Royal College of Pathologists
RCT	Randomised controlled trial
RGS	Regional Genetics Services
RM	Regenerative medicine

RNA	Ribonucleic acid
SCA	Single cell analysis
TALEN	Transcription activator-like effector nucleases
TKI	Tyrosine kinase inhibitor
TPMT	Thiopurine s-methyltransferase
UCL	University College London
VAR	Virtual and augmented reality
WGS	Whole genome sequencing
WSI	Whole slide imaging
ZFN	Zinc finger nucleases

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making science work for health

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The PHG Foundation is a pioneering independent think-tank with a special focus on genomics and other emerging health technologies that can provide more accurate and effective personalised medicine. Our mission is to make science work for health. Established in 1997 as the founding UK centre for public health genomics, we are now an acknowledged world leader in the effective and responsible translation and application of genomic technologies for health. In April 2018 we became part of the University of Cambridge.

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