A STRATEGIC TECHNOLOGY ROADMAP FOR THE UK IVD INDUSTRY

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In vitro diagnostics (IVDs) is the process of testing samples, such as blood or tissue that have been removed from the human body, for medical purposes. It is a thriving industry, worth approximately £90bn globally and £2.7bn in the UK. Moreover, the market is growing, powered by new analytical technologies for clinical applications, innovations within clinical research and the growing incidence of chronic disease.

The UK has a proud record of developing many of the technologies that underpin the global IVD industry. These include paper chromatography which evolved into lateral flow tests, and the genetic sequencing used in around 80% of the world's sequencing systems.

But while the UK excels at research, it lacks the ecosystem, infrastructure and funding for IVD companies to remain in the UK. UK inventions tend to be commercialised by corporations from other countries and there are currently no major IVD companies in the UK. Instead, small to medium enterprises (SMEs) are acquired by global organisations who invest in the development of the core technology, but not always in the UK.

If the UK is to maximise its role in the fast-growing IVD industry, a strategic vision is required that recognises IVD as its own distinct and valuable sector. This report offers that vision.

Designed to run alongside the existing Office for Life Sciences (OLS) strategy for boosting UK economic growth through life sciences, this strategic technology roadmap highlights the global opportunities that the UK IVD industry must address over the next ten years. It predicts the technology developments needed to realise those opportunities and the approaches required to grow businesses around them.

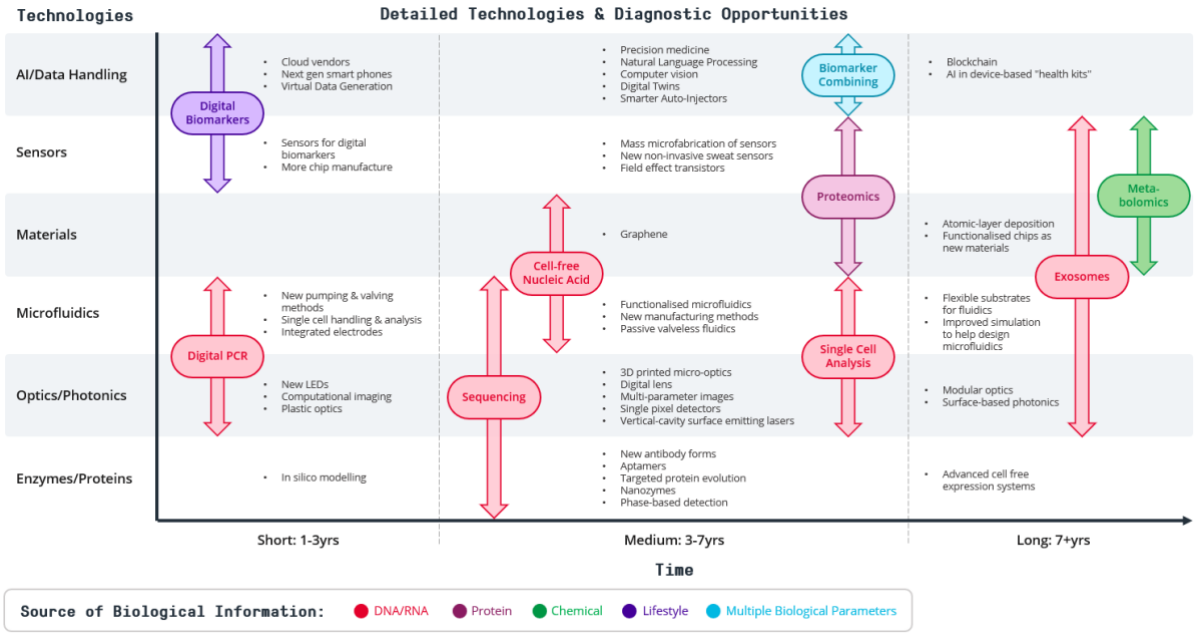
A diverse group of stakeholders contributed to create the following vision statement for UK's future role in the IVD industry:

"The UK will be the industry nucleus for world-leading businesses, with the resources, skills and proven pathways for advancing pioneering technologies into successful data-enabled IVD solutions"

Input was collected from clinicians, publications and patents to define nine key technology-enabled opportunities for the global IVD industry over the next decade. These are:

- Digital polymerase chain reaction (PCR)
- Sequencing
- Cell-free nucleic acids
- Digital biomarkers
- Proteomics.
- Combined biomarkers
- Single cell analytics
- Exosomes
- Metabolomics

To capitalise on these multi-£billion opportunities, the UK must develop specific technologies in materials, enzymes, Artificial Intelligence (AI)/data, optics and photonics, microfluidics, and sensors. This will require the IVD industry to build fruitful collaborations with companies that already have expertise in these areas with increased value sharing, to manage the higher risks and the multi-year ROI.



After discussions with global IVD companies, UK SMEs, big tech, pharma, UK government and NHS stakeholders, seven major challenges were identified:

- Designing, developing, and manufacturing new diagnostic platforms in the UK is limited due to the UK's lack of a suitable ecosystem
- Acquiring the necessary patient samples is too time consuming and costly
- Designing and implementing the clinical studies required to demonstrate value is too complex
- Commercialising new IVD tests across multiple global markets is complex and difficult to navigate
- Securing widespread adoption by clinicians of novel IVD tests takes too long
- Accessing appropriate returns through clinical reimbursement is too uncertain to incentivise new complex tests
- Current financing and investment do not favour the high-risk, high-impact, innovative tests that are needed.

The UK needs to adopt the following strategies to overcome these challenges:

- Boost the IVD industry's profile in the UK
- Create a focused government-led strategy for the UK IVD industry
- Support access to NHS resources during development and commercialisation
- Assist IVD companies through a well-defined and harmonised regulatory pathway
- Develop partnerships for high-risk IVD developments that have defined pathways to clinical use.

New models for investment in the development of high-risk IVD solutions, where the risk and value are shared by partners including SMEs, major IVD companies, pharma and technology players will lead to success. Key to this strategy will be an early, specified path to the clinic with initial payments for tests which solve the most important clinical needs for diagnostics in the UK.

Introduction and Background

Introduction

This report describes a technology strategy for the UK's IVD industry. It highlights opportunities the industry should focus on, technologies it must develop and a clear plan for commercialisation. The goal is to identify technology opportunities that will drive the global IVD industry's development and improve the UK's economic success. The UK IVD industry has much to offer the health and the economic success of the UK but is frustrated by a series of obstacles. The IVD industry includes the tools used in research laboratories to investigate biological samples, which have potential future applications in in vitro diagnostics. This strategy builds on the recommendations of the existing Office for Life Sciences (OLS) strategy while focusing exclusively on the IVD industry.

UK's strong technology research background

In 2021 the global IVD industry was estimated to be worth around £90bn[1], of which the UK contributed 3% (around £3bn)[2]. Many of the technologies at the heart of this thriving industry were pioneered in the UK. For example, the first lateral flow test was launched in 1988 by the UK-based UniPath, now part of US-based Abbott. The sequencing by synthesis (SBS) technology, used in around 80% of the world's genetic sequencing systems, was developed by UK-based Solexa. Solexa was acquired in 2007 for $650m by US-based Illumina, the global leader in sequencing with $4.5 billion in revenues in 2021 and an annual growth rate of around 20%.

Background to this report

Despite having a strong background in IVD research, the UK has failed to capitalise on the commercial benefits of its innovations. Instead, the global IVD industry is dominated by a few large companies that account for 80% of IVD sales. These companies have broad test portfolios and large instrument bases within healthcare systems. The industry follows the "razor-blade" commercial model where revenue is generated through the sales of consumables such as assay reagents which fund the costs of the complex laboratory instruments that run the tests. The companies that dominate the industry do so by extensive sales and distribution networks and significant investment in production capabilities. This market leadership continues over time as the leading companies acquire new smaller companies as the overall market for IVD grows.

The remaining 20% of the market is comprised of smaller IVD companies and larger new entrants from other industries. IVD leads medical device venture financing (over globally £10bn in 2021)[3] driven by new innovations for COVID-19 and cancer testing. Close to 200 new tests for COVID-19 have been approved by the US Food and Drug Administration (FDA) since the beginning of the pandemic. Entrants from other industries range from Amazon to companies centred around research-based life science such as Perkin Elmer and follow the well-trodden path from R&D tools to clinical diagnostics.

[1] Fortune Business Insight, 2021

[2] Mordor Intelligence, 2021

[3] Global data, 2022

The paucity of the UK's commercialisation of IVD was particularly exposed during the COVID-19 pandemic. Unlike other leading economies, the UK was unable to harness any major IVD company to advance diagnostics and the pharma industry had to step in to provide test automation and scientific guidance for national testing systems. This is despite the fantastic efforts of UK SMEs to develop products rapidly during the pandemic.

Potential for growth

The pandemic has created a world in which IVD tests are central to people's lives and companies are responding to this increased interest. The world now faces a difficult economic climate, with a sharper than expected slowdown predicted by the International Monetary Fund (IMF), which forecasts UK GDP growth of 3.6% for 2022 and 0.3% for 2023[4]. Nonetheless, investment in IVD technologies is expected to grow in response to the growing incidence of chronic diseases, such as diabetes, cardiovascular disease, and cancer, as well as infectious diseases, such as gastrointestinal, respiratory and sexually transmitted diseases.

Another major driver for the industry is the ongoing accomplishments of biological research. Biomolecules and biological systems are expected to transform economies, societies and lives over the next few years[5]. The UK will be a global leader in this new era of biology, with spending in life sciences R&D at £2.7bn in 2020, behind only Japan and the US.

With a record of scientific discovery and strong capabilities in biological innovation, the UK is well placed to build leading IVD companies and create new areas of economic growth. This could also improve the competitiveness the UK needs post-Brexit.

To achieve this, the UK needs a strategic vision for the success of its IVD industry. It needs to identify the commercially attractive opportunities to achieve that vision and apply its world-class abilities in science and technology development. Crucially, it also needs to understand and address the challenges of commercialising IVD technologies.

Implementing that strategy will require engagement from contributors across the industry, including global IVD companies, UK SMEs, big tech, big pharma, industry bodies, regulatory experts, and scientists. By combining their skills, capabilities and experience, the UK can become a world leader in the IVD industry.

How this report was developed

The strategy in this report focusses on the global opportunities that the UK IVD industry must grasp in the next ten years, the technology developments needed to realise them and the approaches required to grow businesses around them.

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[4] UK Parliament. GDP - International Comparisons: Key Economic Indicators - House of Commons Library. 2022. Available from: https://commonslibrary.parliament.uk/research-briefings/sn02784/

[5] McKinsey Global Institute. The Bio Revolution: Innovations transforming economies, societies, and our lives | McKinsey. 2020. Available from: https://www.mckinsey.com/industries/life-sciences/our-insights/the-bio-revolution-innovations-transforming-economies-societies-and-our-lives

The strategy includes steps that stakeholders need to implement to grow the industry. It has been defined through contributions from a wide range of stakeholders in the IVD industry, including global IVD companies, UK SMEs, big tech, big pharma, government industry bodies, regulatory experts, and scientists. It provides a focus for the whole UK IVD industry to work together to realise this exciting future.

The strategy was created using a four-step process:

Step 1: Capturing the vision

A vision statement was created through a workshop with diverse stakeholders representing the industry: clinicians, technologists, industry bodies, and NHS specialists. The vision statement's purpose was to inspire and provide focus, and it was considered at all points of the programme to ensure goals were met.

Step 2: Discovering opportunities

An analysis of global diseases helped define the programme's focus. Lung cancer and respiratory infections were used as proxies to identify the relevant broad clinical needs and technologies which could be considered for IVD opportunities. These disease states were selected due to the extensive progress in technology types to address their diagnostic needs. The technology types could be used to answer related diagnostic needs across the other disease states.

Interviews were held with UK and US clinicians to understand the needs for improving existing testing and to create a model for defining and assessing IVD opportunities. An IVD opportunity was defined as where technology solutions could be used to address clinical needs. The model outlines four core needs across all IVD opportunities, three process steps a solution must take, and four success factors on which it can be judged. This model can be used across all disease states.

Nine technology-based opportunities were identified through analysis of recent global intellectual property (IP) and scientific literature across lung cancer and respiratory infections. These opportunities were profiled to understand their strengths, fit with the IVD opportunity model, and the technical challenges preventing them being used for clinical applications. Subject matter experts at Cambridge Design Partnerships (CDP) and CPI were interviewed to identify the technology developments needed to solve these challenges. The experts' fields ranged from biology and materials to optics, engineering, and data science/AI.

Step 3: Define challenges and solutions

A workshop-based strategy development event for stakeholders across the IVD ecosystem built up understanding of the opportunities, defined the challenges to their progression and determined actions needed to solve them. Participants included the global IVD companies, big tech players, government stakeholders, NHS, industry bodies, regulatory experts, scientists, and clinicians.

Step 4: Collaborate to develop clear strategy

Data from the event formed the new strategy, which was reviewed by event participants. Feedback was also invited from stakeholders who didn't attend to ensure consensus and completeness.

Vision

Background

The vision for the roadmap was created as a focal point for everyone involved in the project and for those going on to implement and follow the roadmap. The vision shifts the UK IVD industry to a position where it can target commercially exciting opportunities that fit with the industry's achievements, assets, and capabilities. It lays out an ambitious goal upheld by a united belief in the value success will deliver for the whole industry.

Vision statement

"The UK will be the industry nucleus for world-leading businesses, with the resources, skills and proven pathways for advancing pioneering technologies into successful data-enabled IVD solutions"

Building blocks

The following four themes were considered when building the vision statement.

Theme 1: Winning focus

The UK's underlying strengths are:

- A unique healthcare system, which should enable innovation through national collaboration
- The IVD industry's resilience and adaptability, demonstrated by its response during the COVID-19 pandemic, given the UK's limited number of major IVD companies
- The UK is a major centre for genomics, biomarkers and life sciences
- The real-world evaluation and adoption of the latest science by UK pathology laboratories.

Theme 2: Values

Our values can be met if the UK industry can:

- Build public pride in the UK IVD industry's achievements in reversing and irradicating major diseases
- Provide employment and benefit the environment
- Become the global stage for developing cutting-edge diagnostics products
- Move from "sick care" to "health care"
- Build national companies that become industry leaders.

Theme 3: Aspirations

Our hopes for the industry can be met by:

- Achieving a stronger contribution to gross domestic product (GDP) from IVD
- Having a global impact on unmet clinical needs, for example, autism and mental health
- Creating strong new businesses with the ability to thrive and compete in the global IVD industry
- Reversing chronic lifestyle diseases through diagnostics and digital technologies
- Becoming a global hub for IVD expertise through retention and development of people and businesses
- Making the UK a place where IVD products are developed, manufactured and used across the world.

Theme 4: Goals

The UK IVD industry will achieve its vision if it can:

- Enable personalised medicine
- Reduce costs by moving care from hospitals to primary care, people's homes, and other settings
- Provide early detection to allow early prevention
- Enable the use of data for risk prediction and clinical decision-making to realise desired national healthcare outcomes
- Derive clinical and commercial value from complex multiparameter tests and digital data.

Needs

Clinical needs

To discover the key clinical needs on which to base future growth opportunities, interviews were held with UK and US clinicians in each of the key disease states: respiratory infections, and lung cancer. Over 600 statements were collected from interviews with six clinicians, including lung oncologists and respiratory physicians. Our in-depth analysis showed that every IVD test answers at least one of four clinical needs and possesses three process steps, with four success factors for each step.

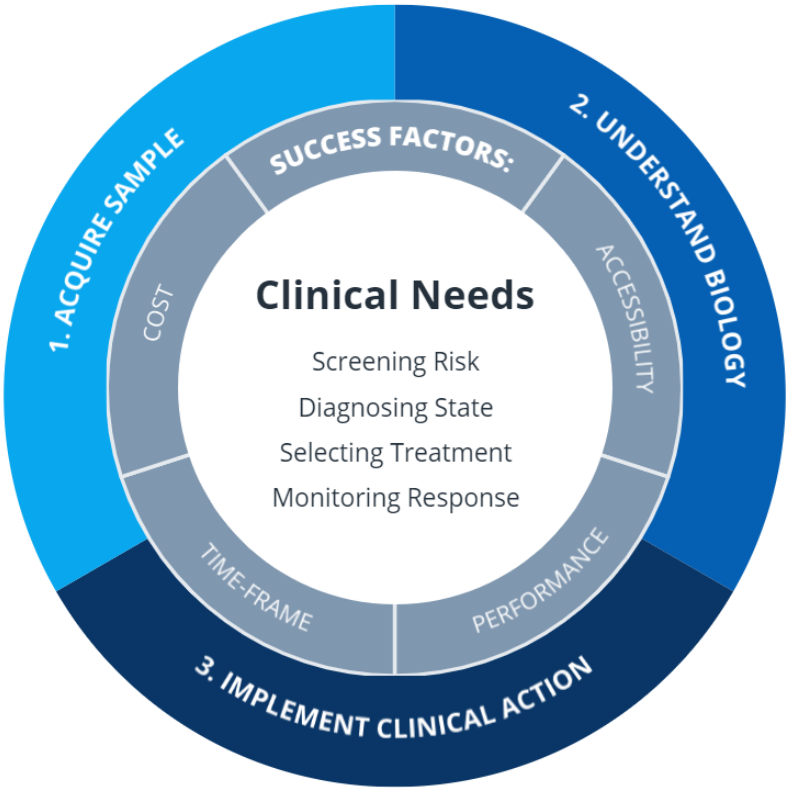

Figure 1 – A model for analysing opportunities and innovations within the IVD industry

Four clinical needs

Every IVD test either screens for personal risk, diagnoses a disease state, selects or monitors treatments.

Need type	Description
Screening personal risk	Identify people at high-risk of developing the disease. Monitor at-risk group for disease development.
Diagnosing state	Precisely understand the disease and its current stage
Selecting treatment	Select the right treatment option for the patient in a timeframe for maximised success
Monitoring response	Track patient response to treatment for efficacy and side effects

Table 1 – Four broad clinical needs that are answered by IVD tests

Screening personal risk

High-risk patients or populations need to be screened to identify people at extreme risk of developing the disease.

In lung cancer, this is carried out using low-dose Computed Tomography (CT) scans for at-risk patients. Most patients are only discovered when they already have Stage 3 and 4 disease, leading to poor treatment outcomes. CT scans sometimes do not identify tumours early enough, so simple, low-cost solutions are needed such as liquid biopsies for detecting tumour DNA or cells in blood samples.

For respiratory diseases, needs involve rapidly triaging patients based on the disease severity of their outcomes as early as possible. Point-of-care tests could be used to decide to admit patients, with more costly hospital stays, or manage them at home.

Quotes from clinical interviews

"The symptoms of lung cancer are unspecific, potentially caused directly by smoking. This means that patients end up in hospital with late-stage cancers"

"Simple tests are required to detect tumours in the lung, as CT scanning does not always pick up smaller tumours"

Diagnosing state

Precisely understanding the disease and its current stage enables healthcare professionals to determine the prognosis. Late diagnosis of diseases such as lung cancer leads to more limited treatment options, such as excluding surgery when the diseases has metastasised to the brain and bones. Classification (e.g. non-small cell versus small cell) and staging through the TNM (Tumour, Node, Metastasis) system, is typically based on traditional histopathological techniques that use invasive tissue samples. Classification of cancers through their genetic mutations – such as Epidermal Growth Factor Receptor (EGFR) – is changing how cancers are managed.

Pathogens must be identified quickly, potentially through point-of-care testing. This can aid the decision process on whether to admit patients into hospitals at higher cost or treat at home. Identifying causative bacteria currently takes too long (48 hours using blood cultures) but is required to understand whether the patient has a serious infection such as bacterial meningitis.

Quotes from clinicians

"Point-of-care testing will become standard in hospitals, with eventually progression into GP's clinics and consumer environments"

"Understanding bacterial infections takes too long today and the molecular testing panels are too limited"

Selecting treatment

The right treatment option for the patient must be selected at the right time for effectiveness – the true meaning of precision medicine.

In lung cancer, increasing numbers of therapies, such as Tyrosine Kinase inhibitors (TKIs), target specific DNA mutations. Chemotherapies are used more often when mutations are unknown. Immunotherapies, when tumours are immunogenic with markers such as PD1, and cell and gene therapies are used, sometimes in combinations with chemotherapies. Tests, based on sequencing, enable many different mutations to be assessed at one time, enabling true precision medicine for a patient.

For respiratory infections, knowledge of the identity of the causative pathogen can be used directly to make treatment decisions. Simply understanding whether the pathogen is a virus or bacterium enables decisions around whether to treat with antibiotics. Furthermore, understanding whether the bacterium is resistant to antibiotics, enables the administration of effective antibiotics and hence minimising the chance of increasing antibiotic resistance. The earlier this knowledge is acquired, the quicker an effective treatment can be given.

Culturing techniques are used to identify the bacterial pathogens and determine their resistance profile, however this takes time and often gives incorrect negative results. Access to more point-of-care testing, with broad panels for different bacteria that enable quicker decisions is seen by clinicians as important. There is a drive for point-of-care testing to be used in primary care to enable earlier treatment decisions.

Quotes from clinicians

"The panels for testing bacteria are limited. Many different organisms are not identified, leading to indiscriminate use of antibiotics"

"It takes 48 hours to culture bacteria, which is too long. If there was a point-of-care test, antibiotics would be used only on bacterial infections and not on viral infections. This would lead to real antibiotic stewardship."

Monitoring response

It is important to know how patients are responding to treatments rapidly, for efficacy, side effects and development of resistance. For lung cancer, regular CT scans are used to understand if the tumours are shrinking, but this only works for large enough tumours and if disease does not progress too quickly. For respiratory infections, management at home is increasingly common. Patients can measure vital signs such as temperature, pulse rate and oxygen, which is monitored by an electronic surveillance system and by nurses.

Quotes from clinicians

“Apps are being used at home. Technology integrated onto arm bands can report on temperature, pulse rates and oxygen levels. A triage nurse can monitor these outputs electronically and request support from physicians as needed. This is enabling management of patients at home, a fast area of growth"

Three process steps

All diagnostic tests have three steps: acquire and prepare the sample; understand the underlying biology; and implement a clinical action.

Process step	Description
Acquiring sample	Collect and process the right sample from the patient to understand their health state
Understanding biology	Analyse cellular and molecular aspects within the patient sample
Implementing clinical actions	Deciding on specific actions to treat the patient based on their biology

Table 2 – Three process steps for any IVD test

Acquire sample

For any IVD test, there will be a core biological sample from which information is acquired. In lung cancer, the highly-invasive tissue samples used to make treatment decisions are difficult to acquire, leading to great interest in non-invasive, regularly taken samples from blood within liquid biopsies.

Understand the biology

The IVD solution will generate an understanding of the patient's biology from the sample. This could include the bacterial species and resistance to specific antibiotics. For cancers, the IVD solution could detect specific mutations, e.g., EGFR mutations, the immunogenicity of a tumour or the resistance mechanisms that are preventing a particular therapy being effective.

Implement clinical actions

A clinical decision can be made from understanding biology. For lung cancer, the sequencing data from tumour samples enables selection of targeted therapies. For infectious disease, tests could lead to understanding antibiotic resistance to guide therapy selection.

Four success factors

There are four success factors that can be used to understand the impact of a novel test.

Success factor	Description
Costs per test	Ensuring costs are not prohibitively expensive for adoption by healthcare systems and patients *E.g. the decision to select a targeted therapy with a value of £100,000 would warrant a more costly IVD test*
Timeframe	Delivering results in a timeframe which does not compromise patient outcomes *E.g. the results from the test have to be available when the clinician is able to treat the patient*
Performance	Measuring scientifically the quality of results from a test *E.g. IVDR refers to performance evaluation of a test to establish or verify scientific validity, analytical and, where applicable, clinical performance*
Accessibility	Minimisation of the expertise and infrastructure required to execute any process step of the IVD test, enabling more regular and widespread usage *E.g. the most accessible test could be considered to be that which can be conducted by an average consumer within their home, from sample collection to implement a simple treatment action, such as using an OTC treatment.*

Table 3 – Success factors for any IVD test

Conclusions

By understanding the clinical needs, process steps and success factors for novel IVD tests, new opportunities can be identified which will enable a compelling vision for the future of the UK IVD industry.

Opportunities

Background

The term 'opportunities' is used in this report to indicate where specific technology types meet the needs of clinicians.

The technology types were identified by analysis of the last three years of published scientific literature and global databases of patent filings. Although the analysis was focussed on oncology and respiratory infections, industry technology experts were consulted to ensure that there were no key technology types omitted which are required for the other leading disease states (e.g. cardiovascular and Alzheimer's disease). Nine technology-based opportunities were selected that could meet clinical needs, answer the vision statement and reach clinical use within ten years. These are shown in the table below:

Opportunity	Application	Timescale for impact
Digital PCR	Modified version of PCR based on splitting the reaction to enable quantitation and detection of rare sequences	Now-3 years
Sequencing	Determining the sequence of the DNA/RNA bases in a sample (also includes whether they have been 'silenced' by methylation)	3-7 years
Cell-free nucleic acids	Nucleic acid fragments released by dying cells into extracellular fluids	3-7 years
Digital biomarkers	Characteristics obtained from digital healthcare technologies that are a measure of a biological process	Now-3 years
Proteomics	The analysis of many proteins simultaneously in a sample	5-7 years
Combined biomarkers	Combining outputs from different diagnostics and clinical symptoms into an algorithmically scored tests	5-7 years
Single cell analytics	The study of cell-cell variation in a population of cells which makes up a tissue, including function, morphology, proteomics and genomics	5-7 years
Exosomes	Very small cell-like particles released into the blood by many cells including tumours and immune cells	7-10 years
Metabolomics	Study of chemicals in a sample that gives a very detailed picture of its physiological state	9-10 years

Table 4 – Opportunities for the IVD industry, their applications and timescales for realisation

Besides the nine technology-based opportunities identified, several other opportunities were not progressed, as they were too incremental or too far from clinical utility. For example, lateral flow technologies can be improved in minor ways which will have minimal effects on clinical outcomes. Protein sequencing, the determination of the amino acid sequences in individual protein molecules, is still in its early stages of technical development, with a lack of clear clinical utility in diagnostics. Spatial biology, the identification of cells, their location, their expression of biomarkers and their interactions, is promising, but the underlying science is still in development.

Technology types

The nine technology types representing the greatest opportunities for the UK IVD industry are profiled below.

See Appendix A for additional data on each opportunity, including strengths, benefits, technical challenges for realisation and feedback from clinicians who are not key-opinion-leaders.

Digital PCR

Definition	Digital PCR is a modified version of PCR that splits the sample into thousands of separate reactions.
Promise	The accurate quantification of DNA and detection of rare sequences against a large background of others.
IVD utility	Cancer diagnostics, treatment of viruses, pregnancy screening and organ transplantation.
Challenges	Current methods require complex disposables and expensive instruments that are not suitable for routine clinical diagnostics with significant sample numbers.
Reasons-to-believe	It is an established research technology that requires relatively simple development to make it suitable for clinical application.

Table 5 – Overview of the opportunity from digital PCR

Digital PCR (dPCR) is similar to conventional quantitative PCR (qPCR) and uses DNA polymerases to copy and amplify specific DNA sequences. qPCR combines the amplification of a specific target sequence in the DNA with its detection, in the same process. Specificity is provided by DNA oligonucleotide primers added to the reaction mix which bind to their target sequence if it is present. Amplification then occurs, with each cycle of different thermal settings leading to a progressive doubling of the resultant DNA products.

dPCR's primary difference from qPCR is that instead of performing a single reaction in, for example, a 100µl reaction tube, the initial reaction mix is split across many hundreds or thousands of separate compartments which undergo the same thermal cycling protocol. After the cycling is complete, the compartments are assessed for a positive result. The number of positive compartments compared to the total number of compartments is used to calculate the precise number of DNA copies in the initial sample.

Sequencing

Definition	Determining the sequence of the DNA/RNA bases in a sample, also includes whether they have been "silenced" by methylation or possess structural variations.
Promise	DNA and RNA holds vast information on a patient's susceptibility to a disease or an infection and also how they respond to medication.
IVD utility	Risk evaluation and management of population groups prior to disease progression. Medication selection and dosage optimisation.
Challenges	Current methods require lengthy multiple separate laboratory processes run on different instruments, which makes integration into efficient workflows challenging. Also requires complex and extensive data processing. Other challenges revolve around the complex considerations for regulatory approval, including the sensitivity of genetic data and clinical validation.
Reasons-to-believe	Several new sequencing methods have been developed in the past few years; it is likely more, and better methods will be invented, developed, and deployed.

Table 6 – Overview of the opportunity from sequencing

DNA sequencing identifies the order of the four nucleotides (adenine, guanine, cytosine, and thymine) that make up DNA in an individual's genome. Sequencing techniques include Sanger, nanopore, and Sequencing-by-Synthesis (Illumina). DNA sequencing can also detect DNA methylation (the addition of a methyl group to a cytosine base) - a biological process that can 'silence' genes and stop them from being expressed. DNA methylation is detected using a minor modification of standard sequencing methods called bi-sulphite sequencing. Sequencing is widely used within research applications, including investigations of unusual or complex clinical cases. The current challenges in costs, turnaround time, data processing and regulatory approval have prevented it from becoming used in routine clinical practice where it has so much value to offer.

Cell-free nucleic acids

Definition	Nucleic acid fragments released by dying cells into extracellular fluids.
Promise	Diagnosis and prognosis of cancer, cardiovascular and neurological disorders, and several other diseases.
IVD utility	Easy, less invasive, repeatable, cost-effective, and able to provide early detection of cancer.
Challenges	Detection and quantification due to its very low concentration and very short lengths. Lack of standardised protocols.
Reasons-to-believe	Several companies are operating in this space and making significant clinical and commercial progress.

Table 7 – Overview of the opportunity from cell-free nucleic acids

Cell-free nucleic acid (cf-NA) appears in the blood after being released from cells that die and rupture. Use of cf-NA is well-established in the pre-natal screening of genetic disorders and is attracting interest in the diagnosis and prognosis of cancer, diabetes, cardiovascular and neurological diseases. However, the widest application is in cancer prediction, screening, monitoring, detecting recurrence, and identification of personalised therapies. Several PCR, next-generation sequencing (NGS) and microarray methods have been developed to detect cancer-specific mutations and alleles in cf-NA. The diagnostic value of cf-NA can be enhanced with the integration of additional biomarkers, proteins, clinical symptoms and data from other diagnostic tests.

Digital biomarkers

Definition	Characteristics obtained from digital healthcare technologies that are a measure of a biological process.
Promise	Cost effective and continuous measurement of the patient's condition, taking healthcare from being reactive to more preventative. Digital biomarkers also help to understand disease better, with new insights for interventions.
IVD utility	Higher impact on neurology and psychiatry; better prospects in the management of cardiovascular disease, metabolic diseases and cancer
Challenges	Identification of relevant data obtained by wearables, inconsistent methods of data analysis and a lack of standardisation. Data protection, data privacy and ownership, inconsistent regulations across regions.
Reasons-to-believe	It represents a low cost and non-invasive way of collecting data that many people have already started to collect for themselves.

Table 8 – Overview of the opportunity from digital biomarkers

Digital biomarkers represent personal biological and behavioural information obtained from digital healthcare technologies. They can be used to measure biological processes and enable the gathering of continuous patient data outside of traditional clinical settings. The role of the smartphone is central to the use of digital biomarkers. Data could also include a consumer's digital footprint or social media activity, being considered a digital biomarker when they can be linked with a healthcare outcome.

A range of sensor technologies and apps are used to collect digital biomarkers leading to the ability to build a model to uncover patient-specific insights. Most common digital biomarkers today include accelerometers, heart rate and speech data, but they are expanding into non-invasive sample collection, e.g. sweat analysis. When combined with other data sources and AI developments, the impact of digital biomarkers over the next ten years could be significant although yet to be fully defined.

Proteomics

Definition	The analysis of many proteins simultaneously within a sample.
Promise	Tissue proteins present the working machinery of the cell, and so the actual cellular components and biomolecules which carry out functions. Their expression levels, functions and structures are key to understanding any of the four clinical needs for any disease state, with a layer of detail untapped today.
IVD utility	A new level of information to be accessed for cancer diagnostics and treatment assessment.
Challenges	Has complex, time-consuming protocols unsuitable for routine clinical use. The proteomic signatures that link to disease progression have not been fully characterised.
Reasons-to-believe	Several almost-suitable detection systems have been developed for the research sector which would need minimal modification to be used in clinical settings

Table 9 – Overview of the opportunity from proteomics

Most clinical protein analysis techniques look at protein types individually. This type of assessment is suitable for binary 'yes/no' decisions or indicating concentration levels. However, for complex diseases like cancer or assessing an individual's physiological state, individual protein analysis does not give a complete picture. Analysis of multiple proteins simultaneously could deliver a clearer picture of the state of disease and its impact on a range of physiological functions.

Proteomics is the analysis of many (thousands) proteins simultaneously and is first and foremost a research activity. Targeted proteomics is the assessment of a smaller subset of proteins (tens to hundreds) and is more applicable to diagnostics. It is much more complex than genomics, PCR and sequencing due to splice variants and post-translation modification which leads there to be a significantly greater number of proteins from that expected from the genome.

Combined biomarkers

Definition	Combining output from different diagnostics and clinical symptoms into algorithmically scored tests.
Promise	Combination increases accuracy of prognosis and diagnosis.
IVD utility	Early prediction of complex multifactorial diseases that require several tests such as cancer, cardiovascular disease, and neurological diseases.
Challenges	Relatively new area that lacks standardisation, references, and guidelines; extensive validation is needed. Alignment with development in different diagnostic areas, deep learning capabilities, and reimbursement.
Reasons-to-believe	Combining multiple different biomarker types together could unlock new clinical information.

Table 10 – Overview of the opportunity from combined biomarkers

Diagnosis of many multifactorial diseases such as cancer, cardiovascular, diabetes and neurological disorders is complex and requires multiple tests for disease identification, disease-stage classification, and treatment decisions. A single biomarker may not provide enough accuracy for diagnosis so multiple tests are needed to make better clinical decisions. The combination of various biomarkers can increase the accuracy of diagnosis.

Several tests have been developed that combine multiple biomarkers from the same individual into a single score, often using a machine learning algorithm to increase the specificity of diagnosis.

Exosomes

Definition	Very small cell-like particles released into the blood by many cell types including tumours and immune cells.
Promise	Exosomes contain RNA, DNA, proteins and lipids that are delivered into their target cells to modify them.
IVD utility	They have a role in cancer formation and progression and so could be useful new diagnostics.
Challenges	Their purification methods are complex, inefficient, and unsuitable for routine clinical use. It is difficult to analyse all their contents simultaneously.
Reasons-to-believe	As a potentially key causative component of the spread of cancer around the body, they could deliver important information of this critical process.

Table 11 – Overview of the opportunity from exosomes

Exosomes and microparticles are very small cell-like particles that are released into the vascular system by a variety of cell types. These include tumours, endothelial cells, platelets, nerve cells and leukocytes and lymphocytes. They vary in diameter from 30nm to 1000nm – far smaller than the usual cell diameter of 7 µm to 20µm.

They carry nucleic acid (miRNA, mRNA, tRNA, long non-coding RNA and DNA) proteins and lipids which can all have activity in their target cell after they have bound to it and delivered their contents.

Their role appears to be to signal to other cells and tissues in the body and regulate or modify their behaviour. Exosomes represent a new high-level regulatory function between hormone signalling and cell-to-cell contact.

Single cell analysis

Definition	Single cell analysis is the study of cell-to-cell variation in a population of cells, including their function, morphology, proteins, and genetics.
Promise	Differences at a single-cell level have an impact on disease which is lost if the sample is tested as a single mass.
IVD utility	Testing for effectiveness of therapies, identifying hard-to-culture bacteria.
Challenges	Limited starting material, differences in capture of molecules and errors in de-multiplexing that cause distortions. Different isolation methods vary in maintaining cell viability. Data analysis challenges from the significant amount of data created.
Reasons-to-believe	Disease often starts at the level of single cells – by detecting these changes it is possible to identify and treat disease before whole tissues and organs are damaged.

Table 12 – Overview of the opportunity from single cell analytics

Single cell analysis is the study of cell-to-cell variation in a population of cells that make up a tissue, including variation in function, morphology, and genetics. These differences are lost in bulk tissue analysis which measures average values across all the cells in a sample. The individual cell differences can have a significant role in disease development. Within each tumour there are distinct cells which differ from each other. Cells interplay differently in space and time, and in their interactions with surrounding tissue. Information from analysis of single cells spans genomics, proteomics, metabolomics, epigenetics, and the transcriptome.

Applications for single cell analysis include making therapeutic decisions for cancer, such as effectiveness of therapies, and characterising difficult to culture microbes (up to 50% of bacteria may not be culturable using standard lab techniques).

Metabolomics

Definition	Study of chemicals in a sample that gives a very detailed picture of its physiological state.
Promise	Permits unique insight into the pathogenesis of disease and drug response.
IVD utility	Enhanced diagnostics through early cancer diagnosis and assessment of treatment efficacy.
Challenges	Has complex time-consuming protocols unsuitable for routine clinical use. The metabolic signatures that link to disease progression have not been fully characterised.
Reasons-to-believe	It has the potential to deliver fast-changing, detailed information on the health and metabolic activity of a patient.

Table 13 – Overview of the opportunity from metabolomics

Metabolomics is the study of how organisms use chemicals to derive energy. The metabolome represents the complete set of chemicals (compounds with a low molecular weight, typically <1,500 Daltons) that a cell, tissue, or organism is using and gives a detailed picture of its biochemical physiology state. Different tissues carry out different metabolic processes at different activity levels and so have individual metabolomic signatures.

The metabolome is studied using nuclear magnetic resonance and gas/liquid chromatography paired with mass spectrometry. These are expensive pieces of equipment with complex protocols but give detailed information on the physiological processes that are active.

Conclusions

There are nine major technology-enabled opportunities ready to be exploited by the IVD industry over the next ten years.

A detailed review of patenting activity showed that the UK is in the top five patent-filing territories for all nine of the identified opportunities. The UK's leading universities, including the University of Oxford, the University of Cambridge and Imperial College London, all have strong patent portfolios in these areas. This is an encouraging base from which to build the vision of the UK being a leader in the global IVD market.

Required technology developments

Background

Many of the opportunities identified as focus points for the UK IVD industry are at an early stage. For example, proteomics, metabolomics, and single cell analysis are all in the R&D stage. Much of their use is in applications for life sciences researchers investigating the underlying biology within disease states. Many of today's diagnostics tools started off as similar R&D platforms. Indeed, many of the leading players within the market started off with a focus on research markets, before developing diagnostics platforms.

A good example of this trajectory is that of polymerase chain reaction (PCR). PCR involved the replication of specific sequences of DNA within a sample, through a process which runs repeat cycling of temperatures of 95°C and 50-60°C. The process is reliant on a specialised enzyme called a DNA polymerase.

PCR was developed in 1983 by Kary Mullis, initially as a manual process. The researcher at the time had to circulate the sample tubes between three different temperature water baths. In its initial Generation 1 format it was costly and time consuming due to the requirement for manually adding new DNA polymerase to each sample at each cycling step. The first major technology development was the application of thermally stable DNA polymerase from the thermophilic bacterium *Thermus aquaticus,* which can survive temperatures of 95°C. Simultaneously, the use of Peltier elements from the electronic industry enabled fully automated heating and cooling of the sample (Generation 2). This enabled the use of automated systems, which are still in use by researchers.

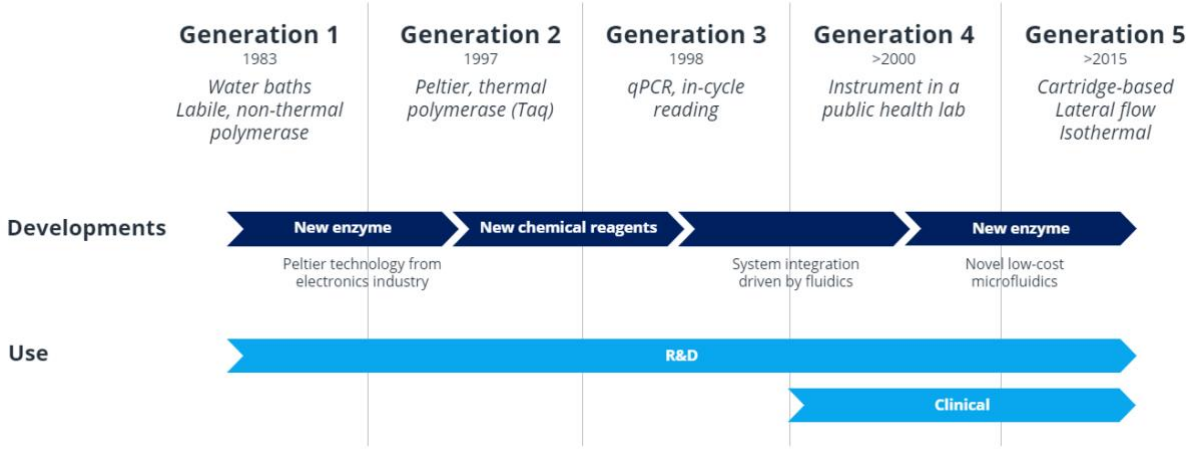

Figure 2 – Technology developments required to bring an IVD solution to market

The next technology development was the use of fluorescently-labelled probe DNA, which in conjunction with a fluorimeter could be used to measure the amount of the DNA sequence produced in real-time throughout the assay process. The previous generation of instruments could not, and required an additional manual procedure (agarose gel electrophoresis) after the reactions had taken place. This new generation of instruments (Generation 3) was quicker and easier-to-use, but they were still only being used in research laboratories.

When the initial sample processing steps were incorporated into the process by using automated pippeting fluidic systems, high throughput instruments were producted that were suitable for use in public health laboratories (Generation 4). These systems are used for diagnostics, processing hundreds of samples per day for infectious disease testing from blood samples, cervical and respiratory swabs.

They are the "work-horses" of clinical diagnostics, with each instrument generating £100,000s of revenue from consumables and reagents. Automation is a key part of the evolution of a new IVD technology and allows it to be easily accessed by clinicians. This lead to the classic "reagent rental" model for the diagnostics industry, whereby laboratories "rent" the instruments for free in exchange for long-term contracts to purchase reagents and consumables.

With the drive towards executing tests near patient bedsides, doctor's offices and even in the consumer's homes, there have been further technology developments. New enzymes have been discovered and engineered to replace DNA polymerases which no longer need thermal cycling to copy/amplify nucleic acids. This updated process is called isothermal amplification, and is one of many technology developments which are enabling a new generation of instruments (Generation 5). Other technology developments which are empowering this generation of instruments are cartridge-based systems which contain all the reagents for the execution of an amplification reaction, using a single patient sample. Many diagnostics opportunities will not progress in this direction with the high throughput instrument being the end-point, and the most important generation in terms of commercial revenue.

To reach routine clinical and commercial use (i.e. Generation 4 and 5), there needs to be a number of technology developments for all of the discussed nine opportunities. These are based on the specific technical challenges that each of the nine face during their development into routine high throughput applications. The required technologies are described below.

Technology developments required for commercialising new IVD tests

The technology developments identified fall into six different areas, all are part of the challenge of creating high throughput automated commercial systems:

- New materials
- New enzymes
- New optics and photonics
- New microfluidics
- AI/data handling
- New sensors

New materials

Technology developments in new materials will enable new interactions between DNA, proteins, and other chemistries.

- Atomic-layer deposition
- Functionalised chips as new materials
- Graphene

New enzymes

Enzymes are essential to the assay chemistries within IVD solutions. Novel solutions for catalysing the reactions conducted by enzymes, could enable new sequencing techniques amongst others.

- New antibody forms
- Aptamers
- Advanced cell-free expression systems
- Long length DNA synthesis
- Targeted protein evolution
- In silico modelling
- Nanozymes
- Phage-based detection

New optics and photonics

Low-cost optical detection systems could enable a new generation of diagnostic products, across many of the discussed opportunities, including sequencing, digital PCR, and single cell analytics.

- Computational imaging
- Digital lens
- Multi-parameter images
- Surface-based photonics
- New LEDs
- Modular optics
- Vertical-cavity surface-emitting lasers
- Single pixel detectors
- Plastic optics
- 3D printed micro-optics

New microfluidics

Improved microfluidic technologies will enable the development of new generation of IVD products, including sequencing, digital PCR, single cell analysis and exosome-based diagnostics.

- Flexible substrates for fluidics
- Integrated electrodes
- Functionalised microfluidics
- Single cell handling and analysis
- New pumping and valving methods
- Improved simulation to help design microfluidics
- New manufacturing methods
- Passive valveless fluidics
- Pumping using non-mechanical mechanisms

AI/data handling

AI, data handling and algorithm development will lead to novel digital biomarkers and enable the clinical utility of diagnostic products, which include sequencing, proteomics, metabolomics, and single cell analysis.

- Digital twins
- Computer vision
- Virtual data generation
- Smarter auto-injectors
- Improved precision medicine
- Natural language processing
- AI in device based "health kits"
- Blockchain
- Cloud vendors
- Next gen smart phones

New sensors

New sensing capabilities for DNA, proteins and other biomolecules could enable opportunities within digital PCR, sequencing, exosomes, proteomics, metabolomics, and single cell analysis.

- Mass microfabrication of sensors
- Non-invasive breath sensors
- Non-invasive sweat sensors
- Field effect transistors
- Flexible organic electrodes
- Sensors for digital biomarkers
- Optical sensing
- Low-cost mass spectrometers
- Higher levels of chip manufacture

Summary

Technology developments within these six specific areas may give the UK the ability to lead within the identified IVD opportunities. The developments may come from new R&D, within the universities, or from companies from other industries in the UK which possess these technologies. These companies need to be incentivised to invest in R&D of their technologies as less of a supplier and more as a partner. Their support is needed to enable these exciting new opportunities for the IVD industry.

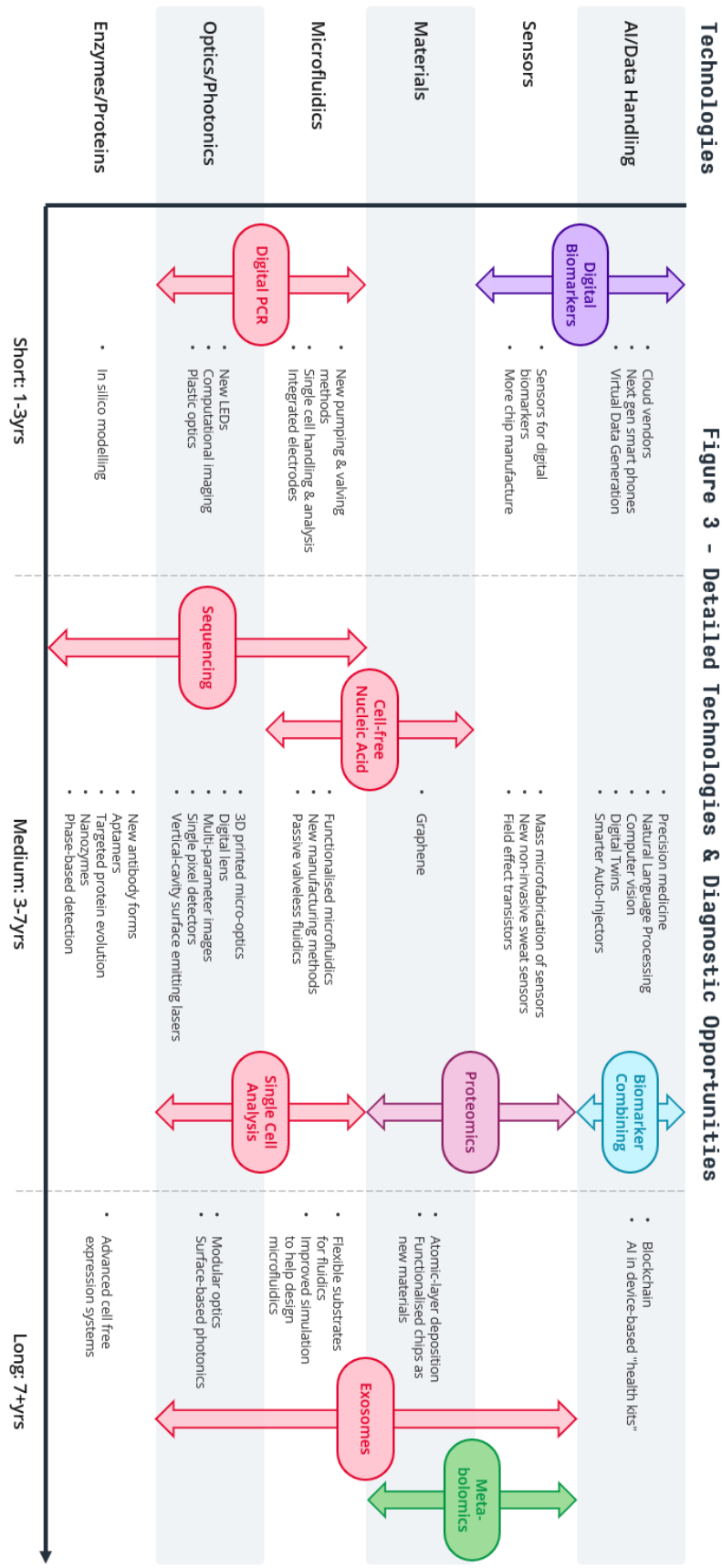

Figure 3 - Detailed Technologies & Diagnostic Opportunities

Challenges

Challenges

Through discussions across the industry, there are seven major challenges that need to be resolved for early-stage technologies through development to commercialisation and clinical use:

Figure 4 - Key challenges for bringing IVD solutions to the market in the UK

Overview of the challenges

Challenge 1: Designing, developing, and manufacturing new diagnostic platforms in the UK is limited due to the UK's lack of a suitable ecosystem.

Current diagnostics is dominated by high-throughput instruments in public health laboratories. They are placed within laboratories by the largest diagnostic companies and their capital investment costs are paid for through long-term "reagent rental" models. The current instruments have large menus for different types of tests (e.g. PCR, clinical chemistry and immunoassay), and vendors typically work to keep their instruments running as many as possible by offering an extensive menu of tests. Due to their significant levels of automation and high throughput, large core labs underpin most diagnostic tests run within a country.

New assay chemistries or technologies need to be implemented on new systems as the existing devices only run specific proprietary tests. The current automated instruments cannot run the tests represented by the new opportunities identified in this report; a full design and development programme is required to build them, often from scratch. The UK does not have the infrastructure for the development of high-value IVD solutions or the skills to build and commercialise such new instrument/consumable platforms. Typically, they are developed by Japanese or US companies. As a result, the SMEs who need new high throughput laboratory instruments to run their new assays do not have access to the necessary manufacturing capabilities.

Challenge 2: Acquiring the necessary patient samples is too time consuming and costly.

Clinically relevant patient samples are vital during the development of new diagnostic tests. However, they are difficult to source, even from biobanks. The samples are usually highly variable, without full and detailed records of their preparation, handling processes, and phenotypic data. The costs of sample acquisition are high due to the rarity of the samples. Clinicians do not generally get involved in the process, as it is not part of their day-to-day activities, and they do not benefit from providing relevant samples to the industry. The regulations do not help either, with factors such as data privacy and the need for detailed permission from patients. It is also very difficult to collect retrospective permission from the patient for any subsequent additional testing on a sample.

Challenge 3: Designing and implementing the clinical studies required to demonstrate value is too complex.

Early stage IVD companies do not have the experience or the skills to design and run high quality clinical studies. Neither do they have an appreciation of the time and cost required. Other issues include:

- Accessing good clinical assistance during trial design
- Selecting clinical sites
- Acquiring Research Ethics Committee approval
- Securing timely patient recruitment
- Understanding existing clinical care pathways
- Collecting the necessary associated patient treatment and demographic data
- Data privacy
- Clinical trial monitoring
- Interpreting clinical statistics
- Real-world logistics of sample collection and transfer.

New IVD start-up companies tend to "learn by doing" which risks ineffective study design, insufficient budgets and timelines, and inefficient engagement with healthcare professionals. Engaging with healthcare professionals is particularly challenging due to the busy nature of their roles and the time required of them to play a major role in a study. Difficulties in study design include providing evidence for significant health economic or commercial value. Intermediate proxies are then required, which makes future reimbursement assessments challenging. Particularly difficult are the trials for rare or short-lifespan diseases, which are challenging to set up and run due to the complexities of multi-site trials and the limited time available for patient recruitment.

Challenge 4: Commercialising new IVD tests across multiple global markets is complex and difficult to navigate.

Global territories have different healthcare infrastructures and regulations to meet their different health priorities and different risk/benefit profiles due to the different needs of their population. Countries and their regions also have differences in their technology and sustainability standards (e.g. connectivity). These differences create a significant barrier which favours global players with the expertise and funding to work through them.

Re-imbursement pathways are complex and poorly understood within companies which causes a lack of clarity on which markets they should sell to. Companies do not understand the costs of acquiring regulatory approval and therefore do not raise the necessary funds to conduct the studies. The US is much clearer on its requirements which encourages IVD companies to target this market. Idealnew technologies would be developed to meet the most stringent regulatory requirements across their target markets – but this is often hard to determine for SMEs. There is also confusion around clinical validity and how regulatory authorities view a new technology. The time taken to navigate these difficulties can threaten the survival of SMEs as their funding diminishes.

To navigate the global and local complexities of the regulatory environment, SMEs need expert advice, which can be difficult to access in a timely and economical way. There has been a huge reduction in the UK of notified bodies (there are currently only three) and consequently access to advice around both the current significant regulatory changes and device approval is difficult.

Challenge 5: Securing widespread adoption by clinicians of novel IVD tests takes too long.

It is hard to bring new tests into the NHS as it is a protocol-driven organisation. Clinicians can be too busy, risk averse, unwilling, or insufficiently knowledgeable to change their practice and adopt new tests/technologies. The procurement processes are extensive and hard to change, even if clinicians support the test. Proving the cost-benefits for the NHS is difficult, and the large number of separate NHS trusts make it even more so. Significant time and effort as well as costs are required to enable test adoption. There is currently no specific IVD champion to communicate at a governmental level on the value of tests to patients.

Challenge 6: Accessing appropriate returns through clinical reimbursement is too uncertain to incentivise new complex tests.

It is extremely challenging to generate the evidence required to demonstrate clinical utility for a test across the many different global markets. There is a perception that IVD tests represent low-value compared to therapeutics. This is reflected in that treatments are paid for on the basis of the number of years of healthy living that they give a patient, whereas diagnostics cannot access this value-based payment approach.

Even within the UK, a single territory, the NHS is not centralised, and hospitals need their own evidence to adopt a new test. The cost-of-sales becomes extremely high when representatives must target the right people in clinical units in many different NHS trusts across the UK to generate sales of a new test. In contrast to treatment approaches, which are defined in a national formulary, there is no obligation to standardise which tests should be used across the healthcare system.

The NHS can take a very long time to adopt new tests and technologies. This is partly because the NHS pathways and associated patient journeys are complex but also because there are silos within the budgets in the NHS, where different departments each own different budgets. This fragmentation makes it difficult to capture the value generated by compelling new diagnostic tests as an increase in cost in one silo is viewed negatively even if it leads to a larger saving in a separate budget.

The current NHS procurement framework favours solutions that offer discounts, which is only feasible for the larger industry players. These players are also favoured by the high-risk, long-term development timelines of new innovative tests which, due to the time they take, risk the survival of SMEs.

Challenge 7: Current financing and investment do not favour the high-risk, high-impact, innovative tests that are needed.

Innovative SMEs do not receive enough funding to complete the development of cutting-edge technologies. Typical funding routes are via Venture Capitalist or Angel investment, grant funding, self-investment, or collaborations with global companies. The level of funding available can only deliver part of the investment required – and not enough to fund the path to commercialisation (e.g. £2-3 million versus £50 million). Investors prefer their SMEs to be closer to the "tipping" point of proving commercial value when the risk on their investment is acceptably low.

The standard model in the UK is for start-ups to develop the technology around established biomarkers, and then sell to one of the larger players within the IVD industry. Small SMEs seeking funding often have incompatible financial needs that do not fit with how the larger companies run their budgets and investments. When collaborating with SMEs, the larger companies can struggle to develop a mutually beneficial deal. SME expectations regarding management of the partnerships and funding are not aligned with the preferred risk and reward mindset of the big companies funding the project.

Pharmaceutical companies often request the development of supporting companion diagnostics by the larger IVD players when their drug has reached Phase 2 clinical trials. The value of the high-cost pharmaceutical treatment is not shared with the IVD company.

The providers of enabling technologies that can unlock some of these IVD opportunities are from other industries, e.g. big tech and electronics. They do not partner directly in the research and development of the technology, acting instead as component or material suppliers. Investment is needed to develop their technologies (ranging from materials to algorithms) to make the test work, but they do not receive funding for its development and hence are not incentivised to invest as they do not share the test value or intellectual property (IP).

Opportunities such as single cell analysis have very compelling potential rewards, with high test prices and volumes. But the scale of investment required is prohibitively high for one company to carry on its own. This results in the inability to move forward with some of the game-changing, high-risk opportunities for the IVD industry.

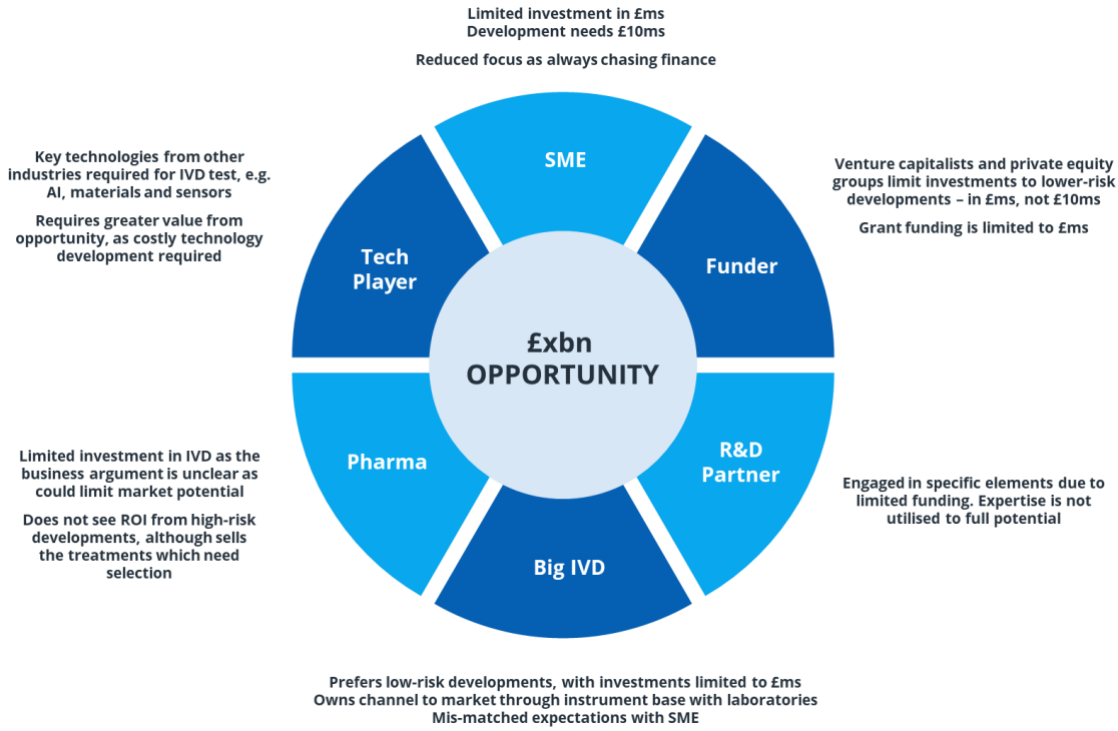

Figure 5 - Challenges in the current model for the development and investment of new opportunities within the UK IVD market

Strategy

A vision for the UK IVD industry

"The UK will be *the* industry nucleus for world-leading businesses, with the resources, skills and proven pathways for advancing pioneering technologies into successful data-enabled IVD solutions"

Today, most start-up based IVD innovations initiated in the UK are acquired by major global companies after they have demonstrated initial technical feasibility and performed limited clinical evaluation. Also, the major IVD companies are based outside of the UK and do not invest in R&D and manufacturing within the UK.

There are several major obstacles for IVD companies as they develop, test, manufacture, gain approval and commercialise new tests. Solving these challenges will be a key part of driving the UK industry towards the vision set out above.

Strategic planning

To realise the vision for the future of the IVD industry, the UK should adopt a five-part strategy.

Figure 6 – The five steps to realise the vision for the future of the IVD industry

Within each of these steps, there are several separate actions to be implemented.

1) Boost the profile of the IVD industry in the UK

The UK IVD market is fast-growing with several clear opportunities to excel on the global stage. The UK's Office for Life Sciences (OLS) has created a strategic overview of how life sciences can boost economic growth in the UK, but the report is primarily focused on therapeutics rather than diagnostics. The UK must implement the findings of the OLS strategy and also focus specifically on IVD. To help achieve this, the IVD sector needs to raise its profile. This is especially relevant now as the public is more aware of the role of diagnostics and investors have a strong interest in IVD opportunities.

Specific actions recommended include:

A. Appoint an IVD champion to promote IVD at government levels

Select a "heavy hitter"... influence decision makers... promote cost benefits beyond NHS

The role would be to promote the value of IVDs at senior levels, linking to a parliamentary group focussing on return on investment (ROI) for IVD. Promoting cost benefits to the treasury, instead of the NHS, could drive uptake of new tests. The appointed person would have a strong reputation to help influence decision-makers. This could be linked with a new or existing parliamentary group to focus on ROI in new IVD technologies and tests. It is thought that proving cost-benefits to the treasury in addition to the NHS may be a more effective way of uptake of new tests.

B. Drive uptake of new IVD tests in the private sector

Adopt new tests within private sector... demonstrate value and utility... promote interest in NHS adoption

Adopt new tests within 1-2 trusts.... demonstrate value and utility.... promote interest in adoption throughout the NHS

Use of tests in the private/consumer driven (B2C) sectors could establish their value and utility, building interest and supporting data for the test to be adopted by the NHS. NHS adoption would enhance the potential for global adoption, due to international perception of the high standards and "brand" of the NHS and National Institute for Health and Care Excellence (NICE).

An alternative would be to demonstrate value by grant-funded studies for the IVD test in one or two NHS trusts, through which value and utility can be demonstrated for adoption across the NHS.

C. Build support for new IVD tests by clinicians

Create stronger communications between companies and clinicians... educate on test benefits... change mindsets

IVD providers need to drive and support the education and training of clinicians on the benefits offered by new solutions – even at early stages of their clinical development and adoption. This will help to change the mindsets of clinicians when adopting new tests in their practice with a greater appreciation of their utility and value.

2) Create a focused government-led strategy for the UK IVD industry

The UK has been successful at the scientific innovations which underpin potential new IVD tests, with IP leadership positions within all the key future opportunity areas for IVD. The industry needs to have a clear direction that is co-ordinated between government policies, regulations, healthcare organisations and IVD companies.

Specific actions include:

A. Define requirements for solutions to answer specific clinical needs

Create "target test profiles" to answer clinical needs… guarantee payment for success… grant fund to support development and growth in the UK

Government and the NHS/NIHR (National Institute for Health and Care Research) must work together to define "target test product profiles". These specifications will define what is needed to answer the short to long-term needs of clinical pathways. They should provide specific targets for IVD companies to develop against and guarantee payment for providing the benefits required. The profiles will also enable companies to check whether their products meet healthcare needs. Having such targets will stimulate both R&D activities and investments in the UK, through greater confidence in commercial success.

Significant non-dilutive grant funding should be provided to companies that respond to the target profiles, helping them retain their capital and avoid acquisition by foreign companies. This funding should be significantly greater than the £100,000 grants from the Small Business Research Institute (SBRI), to support clinical trials, and the £2m grants from Innovate UK. This is a similar concept to the US Defence Advanced Research Projects Agency/Biomedical Advanced Research and Development Authority (DARPA/BARDA) approach.

B. Attract international IVD companies to the UK for development and manufacturing

Provide incentives… create accessible integrated supply chains for design, development, and manufacturing

The government should adopt policies to make the UK more attractive to IVD manufacturers. A very limited amount of manufacturing or high-value R&D is carried out in the UK by global IVD companies. The manufacturing capabilities required to support the industry are limited and are not being developed to create the end-to-end process and the necessary supply chains. Government-led organisations such as Catapults and the CPI could potentially be used to create simple to access full scale commercial manufacturing services. The Government could support the development of an integrated UK supply chain that can design, develop, and manufacture reagents, consumables, and instruments. Of particular interest would be the large high throughput systems that currently perform much of the automated testing in clinical laboratories. The supply chain approach could be based on linking a network of smaller companies creating the capability between them.

To drive these developments, there need to be greater incentives for companies to develop and manufacture in the UK. Examples include the low-tax approach used to stimulate re-location of medical device companies to Ireland. Other incentives could be provided for companies that train workers. Policies and legislation to remove import and export barriers would also be beneficial.

C. Create a step-by-step guide to provide best-practice for test commercialisation

Industry consultation to understand challenges… develop guide for funding, studies, approval, and reimbursement

Government-led organisations should create an industry-standard guide with step-by-step directions to guide IVD companies on the commercialisation process in the UK. Currently, it can be unclear, with companies having to discover the process for themselves. The guide should have a checklist which specifies all the steps and data requirements. A consultation within the IVD industry – by the British In Vitro Diagnostic Association (BIVDA) for example – should set out what information the IVD reimbursement guide should contain. The guide requirements can then be discussed with regulators, government, and the NHS, to determine how best to develop the guide.

It would also include guidelines on how to demonstrate value in different clinical areas, and what "success looks like" to secure clinical adoption – especially for complex tests. It would additionally cover access to funding for clinical studies, Research Ethics Committee (REC) approval, reimbursement, and NHS adoption. Post initial adoption, the economic value delivered by the test should be demonstrated to drive further uptake. The NHS/UK could be used to demonstrate the value of the new IVD test. The data generated could be used to drive its use globally.

D. Reimburse diagnostics based on value

Define how to articulate a business case for value-based reimbursement among stakeholders

IVD companies struggle to demonstrate the value of tests, in contrast to pharmaceutical companies which recoup their R&D spend based on quality-adjusted life years (QALYs) delivered. The case for value-based reimbursement must be made for diagnostics.

3) Support access to NHS resources during development and commercialisation

There are many challenges for companies in accessing and using the NHS – both during test development and for commercialisation. These challenges include accessing clinical data, getting samples, setting up clinical trials, and selling products across the NHS. A series of initiatives would significantly help UK IVD companies on their route to success. Specific applications include:

A) Establish and facilitate access to clinical samples during test development

Build a universal opt-out service for sample remnants… Initiate with government funding… Migrate to subscriptions for major companies/one-off payments for small companies

An opt-out service should be developed with residual sample remnants (both fluid and tissue) across all hospital groups, which could then be utilised by companies. An example could include access to defined panels of blood from different patient demographics with anonymised clinical data – e.g. 50 blood samples from men and women over 50 with diabetes and cardiovascular disease (CVD). Patients, if they preferred, could opt-out of the service. The information on the sample types could be stored in an on-line digital system with standardised data storage. The system could store requests for different sample types, allowing IVD companies to link with clinics providing the required samples, potentially with the help of university Technology Transfer Offices. UK biobanks do exist but they are intended more for research use than commercial use. The sample retention/collection system could be made financially sustainable via a subscription from big companies and one-off initial payments for small companies – with initial support from government funding. It should prioritise usage for UK-based IVD companies.

B) Maintain a public, renowned clinical trial toolkit for growing IVD companies

Build a 'toolkit' website with clear direction for clinical trials… publicise… maintain by nominal payments for access

The toolkit should be a government website which specifies the steps required throughout the process, identifies the existing available relevant infrastructure, expertise, and skills in the UK, and shows benchmark costs to allow accurate financial planning. It should also contain a matchmaking system, to enable connections between start-ups, healthcare practitioners (HCPs), contract research organisations (CROs), legal firms, incubators/accelerators, consultancies, and others. The toolkit should be written by people who have significant experience of running clinical trials. It should become a definitive single source for "approved information" for running clinical trials in IVD.

The website which holds the toolkit could also provide a mechanism for bringing and supporting mentors from universities, the NHS, and other companies to support IVD companies during their clinical trials process. Mentors can provide resources, contacts, advice, and a legitimacy for investors.

Potential owners of the toolkit could include the National Institute for Health and Care Research (NIHR) as it builds on what they already do today. The toolkit needs to be heavily publicised, so that the whole industry knows that it is the definitive resource for executing clinical trials.

Funding would be from government during the set-up stage. Mentors would be incentivised by publicity, future work, and equity. Eventually, the toolkit would become self-funded by its users with nominal fees for access.

C) Create a public list of clinicians available to support clinical trials

Identify clinical key opinion leaders (KOLs) to support IVD development… Centralise public list

Finding clinicians to support clinical trials is not an organised process and is difficult for many small IVD companies. A public list of clinical KOLs should be available for championing new tests so that they can assist with early shaping (both product and usage) during development to ensure fast and full uptake.

D) Develop answerable opportunity profiles around unmet clinical needs

Identify unmet needs collaboratively with healthcare and industry… develop opportunity profiles to guide innovation

Healthcare, industry, and academia should work together to identify the unmet UK-based clinical needs, and then define product requirements to meet them. These should be captured as UK-specific product profiles, which include identification of the correct NHS stakeholders for the trials. There should also be an assessment of the health economics, its value in the UK plus the required clinical data to complement whatever is already available. This will encourage a focus on the development of technology which answers clinical needs directly, providing clinical value and support for public health. A streamlined, transparent regulatory process should be defined, to manage costs and timelines, in partnership with the development of these profiles. This pathway should be clearly stated in the profiles.

E) Mandate consistent use of impactful IVD solutions across NHS trusts

Build a list of clinical needs… Match IVD solutions against needs… Circulate for mandated use across the NHS

Current usage of IVD tests across the NHS varies. It is important to ensure that they are used consistently across all NHS trusts. Usage must move away from guidelines to mandated use. The success of mandated use has been demonstrated during the pandemic, with a centralised procurement system for all tests.

F) Create NHS centres of diagnostic excellence

Create programme to push quicker adoption of high-risk solutions… Co-ordinate with MHRA and procurement teams for success

There needs to be a new programme, beyond the current innovation managers, to introduce, adopt, and adapt to new innovations within the NHS. The centres should drive earlier adoption of new technologies than the existing mechanisms, such as digital technologies, where progress has been slow. The focus for these centres should be high-risk initiatives/technologies. The post-Brexit Medicines and Healthcare product Regulatory Agency (MHRA) may be able to take its own decisions and improve the regulatory process. The NHS procurement teams must be educated on the benefits of using new IVDs to drive forward the work of these centres. This may necessitate changes in the procurement financial endpoints (one, two, and five years) to provide enough time to demonstrate benefits.

4) Assist IVD companies through a well-defined and harmonised regulatory pathway

There is great uncertainty in the current and future regulatory environment due to the extensive changes in regulations – Brexit and transition from the in vitro diagnostic medical devices directive (IVDD) to in vitro diagnostic medical device regulation (IVDR). This is significantly affecting the IVD industry and threatening the UK's access to tests as it represents only 3% of the global IVD market. If the environment is too challenging, manufacturers may not develop or launch products in the UK. Specific actions include:

A) Define clearly IVDR harmonised regulatory pathways

Reduce complexity in UK regulations… match complexity of competing markets

The current direction of regulatory pathways in the UK is unclear. There is a clear risk to the availability of IVD solutions in the UK if the regulatory pathway is more complicated than IVDR. The EU represents around 25% of the global market, and as such is a more important commercial target for IVD companies than the UK.

B) Facilitate access to high-quality regulatory advice

Implement a government-body to advise on global regulations… Increase availability of supporting notified bodies and funding

It is currently difficult and expensive for companies to gain advice on regulatory processes. This advice is needed at an early stage, so that companies can attain the correct level of funding. Furthermore, IVD companies struggle with the complexity of how the different global markets vary in their regulatory requirements. Companies and their investors need clarity on end-to-end regulatory processes, but do not have an easy or low cost way to do this. On-line guidance on the process with step-by-step guides would help companies to navigate through the maze.

A government-funded body should be available to direct companies on how the regulatory requirements differ within different markets (e.g. MHRA or Innovate UK). The Department for International Trade (DIT) could be boosted to have sufficient funding and incentives, alongside tax breaks, to help new companies overcome the regulatory hurdles. An increase in the number and availability of Notified Bodies in the UK would certainly help. Additional programmes, similar to the recent Health TRIP which allowed UK SMEs to access up to £30,000 to fund regulatory advice, should be implemented.

C) Simplify regulations to boost IVD innovation

Create a "minimal level of acceptance" to demonstrate value before full development… Collaborate with industry and healthcare to define simplified but effective regulatory processes

The current regulatory environment needs to be modified to support UK patients and the IVD industry – in line with the OLS vision statement. For example, verification and validation is a real challenge for first applications of breakthrough new technologies. An alternative may be a "minimal level acceptance" to allow the technologies to demonstrate initial value and then to be assessed in a more rigorous way when more developed. The UK diagnostics community (industry, users, and patients) should work with the MHRA to determine how the approval of new technologies could be facilitated.

D) Review IVD regulatory data simultaneously for multiple markets

Upload companies' regulatory data onto a website… review by individual countries to indicate required changes

A website should be created for uploads of companies' verification and validation reports. Individual countries could review this data to assess the additional requirements needed for the companies to meet their requirements. This would increase efficiency, as companies do not have to start again for each country. This model should be tested on IVDs with relatively simple regulatory requirements, with limited modification necessary to meet the needs of individual countries. The process could then move onto more complex tests, where the changes in requirements would be more extensive.

E) Improve efficiency of regulatory decision-making

Harmonise regulatory standards and data requirements between countries and companies… Work with industry and global bodies to agree

The time taken to set up new regulatory systems such as the International Medical Device Regulators Forum (IMDRF) and the Medical Device Single Audit Program (MDSAP) should be shortened. Further advances could be made by harmonising regulatory systems under the leadership of global bodies such as the World Health Organisation (WHO). Interoperability standards should be agreed between the different companies and lead to standards in data. The new standards for new complex technologies should support current clinical pathways or creatively disrupt them – health economics should be included throughout the evaluation and assessment process.

5) Develop partnerships for high-risk IVD developments that have defined pathways to clinical use

Different parties who could gain commercial value from novel IVD should be working together to reduce the financial risks associated with the development. They should form integrated partnerships where they all share the value of the IVD opportunity, including the IP and knowhow. Any partner could reduce their share of value by selling to other parties within the integrated partnership. Different partners could adjust their number of shares and investment in the partnership, according to their needs.

All the partners, the SME, investors, large IVD companies, tech players and pharma companies, would work together to meet the Target Product Profiles (TPPs) or Opportunity profiles defined to address definitive short-term, medium-term, and long-term needs within the NHS. Clear targets with guaranteed payments on delivering the benefits would stimulate both R&D activities and investments in the UK, through greater confidence in commercial success.

Figure 7 – A new model for investment and development of IVD opportunities in the UK IVD market

Risk is significantly reduced through the guarantees for payment on success. It is also reduced by the sharing of the risk by several different parties. The reduced risk enables the SME to attain the investment from funders, large IVD players, the pharma company, and the tech player.

The funder, if an investor, is likely to take a greater risk, and invest more deeply through increased confidence by sharing the risk with other parties. The UK government could also invest in the partnership to grow the UK economy. The big IVD player can bring the new tests to market and increase their investment due to the overall reduced risk. The pharma player can invest due to this reduced risk, getting access to new biomarkers to enable real precision medicine. The tests from these high-risk IVD developments could justify the usage of high-value drugs, providing a commercial rationale for the investment for the pharma company.

The tech player will be able to develop their solutions to address the market opportunity directly and attain some form of value share which would enable them to partake in development of the test with the other partners.

The role of the R&D partner would be to act as an integrator who can uniquely define the project, filling resource needs and technical gaps. They would not share the value of the partnership, being paid through their traditional fee-for-service model. They could be paid initially by government funding, seed funding, or

other potential partners to initiate, lead, and drive the partnership. The role of the integrator could be to bring other parties to support the integrated partnership, ranging from financial analysts to experts in data analysis.

Conclusions

The UK has the potential to become a world leader in the high-growth IVD industry. It has an unrivalled legacy in scientific excellence and innovation, and is ideally placed to capitalise on nine potentially lucrative opportunities for the global industry due within the next ten years. Progress towards this goal, however, is hampered by several surmountable challenges which the whole industry agrees are impeding commercial success. From R&D and infrastructure to investment and commercialisation, the UK's problems lie, not in the development of innovative technologies, but in bringing them to market.

The five-step strategic plan within this report aims to meet these challenges. The plan has been built collaboratively with the whole industry and its partners – potentially the first time this has been possible. It will provide a platform for the industry to centralise its activities and make a major contribution to UK GDP. Partnerships must involve the major pharma companies whose treatments must be selected and monitored through IVD solutions. There also needs to be a greater role for technology providers who develop the technologies (from enzymes to algorithms) that make novel IVD solutions possible. There has been strong interest both within the UK and globally on the development of this strategy. Global interest has centred around unlocking these major opportunities which could drastically improve healthcare, but are considered as high-risk to investors.

We must now continue this spirit of collaboration and centralisation to implement this strategy. Key will be new models for investment in the development of high-risk IVD solutions, where the risk and value are shared by partners including SMEs, major IVD companies, pharma, and technology players – with a clear, re-imbursed path to the clinic in the UK for tests which truly answer clinical needs.

Appendices

A Project partners

B Disease states

C The technology opportunities

D Technology developments

E Glossary of terminology within the Vision Statement

F Acknowledgements

Appendix A: Project partners

CDP developed this report in partnership with CPI and ABHI

CPI

At CPI, our vision is to enable a healthier and more sustainable future through deep-tech innovations. Our mission is to catalyse advanced technologies for manufacturing solutions that benefit people, places, and our planet.

CPI acts as a catalyst bringing together academia, businesses, government, and investors to translate bright ideas and research into the marketplace. We do this by giving our customers access to the right experts, equipment, networks, funding and more – connecting the dots for effective innovation.

We are a leading independent deep tech innovation organisation and a founding member of the UK government's High Value Manufacturing Catapult (HVMC). Established in 2004, our teams apply their many years of experience to ensure that every great invention gets the best opportunity to become a successfully marketed product or process. We work with our partners across diverse markets in the UK and around the world, driving their innovations forward and helping them to reduce the risk and cost associated with product development.

The main markets of focus for CPI are:

- Pharma
- HealthTech
- Sustainable Materials
- AgriFoodTech
- Energy Storage

CPI was the overall project lead for the Health Technology Regulatory and Innovation Programme

More information about the programme can be found here: https://www.uk-cpi.com/HealthTech-regulatory-support

More information about CPI can be found here: https://www.uk-cpi.com/ and https://www.uk-cpi.com/HealthTech

ABHI

ABHI supports the Healthtech community to provide products and services that help people live healthier lives. As the voice of the industry, we show the value of health technology and overcome barriers to people benefitting from it now and in the future. Members include leading multinationals through to small and medium sized enterprises (SMEs). We represent the healthtech industry to key stakeholders, such as governments, healthcare systems, and regulators.

ABHI supports the healthtech community to provide products and services that help people to live healthier lives through:

- Shaping digital health
- Leading access to healthtech
- Informing regulation
- Guaranteeing trust
- Supporting sustainability
- Building UK diagnostics
- Promoting equality, diversity, and inclusion
- Fostering growth.

More information on ABHI can be found here: https://www.abhi.org.uk/

The training developed as part of this programme by ABHI can be found here:-
https://www.abhi.org.uk/what-we-do/informing-regulation/the-regulatory-roadmap/

Cambridge Design Partnership

Cambridge Design Partnership is an end-to-end innovation partner, propelling global brands and ambitious start-ups to success.

We build breakthrough products and services – from insight to ideas, prototypes to production – bringing innovation to life. Our teams are multi-disciplinary, uniting scientific rigor, design ingenuity, and engineering excellence for healthcare, consumer, and industrial clients.

People-centred, deeply collaborative, and – above all – expert, we're uniquely positioned to shape the future for consumers, patients, and industry. Even our ownership model is innovative: We're 100% owned by our employees, ensuring an open culture and a total commitment to your project's success.

Funding

Innovate UK

Innovate UK is the UK's national innovation agency. We support business-led innovation in all sectors, technologies and UK regions. We help businesses grow through the development and commercialisation of new products, processes, and services, supported by an outstanding innovation ecosystem that is agile, inclusive, and easy to navigate.

More information on Innovate UK can be found here: https://www.ukri.org/councils/innovate-uk/

Innovate UK's Health Technologies Regulation and Innovation programme

The Health Technologies Regulation and Innovation programme (HTRIP) was funded by Innovate UK, providing £7m to support UK SMEs in this challenging market. It was made up of the following initiatives:

1. Non-dilutive grant funding for SMEs to receive advice and support for regulatory experts

A funding scheme of £6,390,000 of grants to UK SMEs was delivered by CPI. UK SMEs developing medical devices were able to apply for grants of up to £30,000 to enable them to access regulatory advice and support.

2. Training programme

The Association of British Healthtech Industries (ABHI) delivered a series of webinars to help UK SMEs who lack regulatory experience or training.

3. IVD roadmap development

CPI and Cambridge Design Partnership developed an actionable technology and capability roadmap for IVD to support innovation planning and guide future UK interventions in IVD. This report summarises the output from the roadmap.

4. Insights

All recipients of the HTRIP grant funding were requested to complete a survey on their business and outline the challenges they were facing in the development and commercialisation of their products and services. ABHI also held a series of round table workshops across the UK, where stakeholders, SMEs, and others discussed their challenges. A further short survey of SMEs was also run to provide additional information.

Appendix B: Disease states Focussing on disease

Background

Opportunities within the industry come from answering needs within specific disease areas, including early-stage detection (screening), diagnostics, treatment selection, and monitoring efficacy of the treatments. The breadth of areas which could be covered are expansive; from common conditions such as diabetes to rare genetic diseases such as mitochondrial diseases. The vision for the UK IVD industry is focussed on improving patient outcomes while delivering commercial revenues. It is also focussed on being commercially attractive to investors and IVD businesses to operate within UK shores.

For these reasons, the roadmap must focus on diseases with high global incidences and/or those that could deliver significant commercial value. The disease states that are focused on must also be those in which IVD solutions can make an impact through the value of the new data that they can deliver.

Value from diagnostic solutions can be achieved by reducing numbers of deaths and/or the impact of the disease state on the patient. Two measures can be used to assess this value:

- Mortality rates: these are the number of people who die each year per 100,000 population. It gives a general measure of the gravity of the impact of a disease on a population.
- Disability Adjusted Life Years (DALYs): A time-based measure which combines Years of Life Lost (YLLs) due to premature mortality and years of life lost due to time lived in states of less than full health, or years of healthy life lost due to disability (YLDs). One DALY represents the loss of the equivalent of one year of full health. DALYs are particularly useful to compare burdens that cause premature death but limited disability (e.g. drowning) to diseases that do not cause death but do cause disability (e.g. retinal cataracts).

Mortality rates

Ischaemic heart disease, stroke, and lower respiratory infections are the top causes of death across all regions.

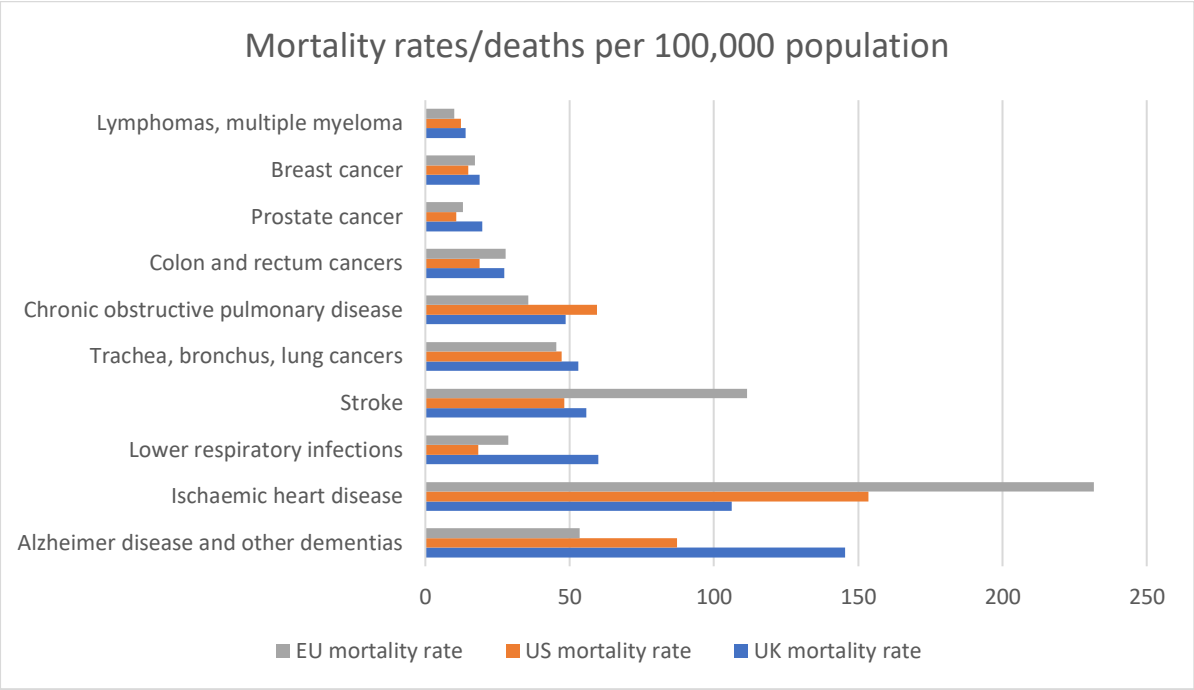

Table 14 – Mortality rates of different disease states across the EU, US, and UK

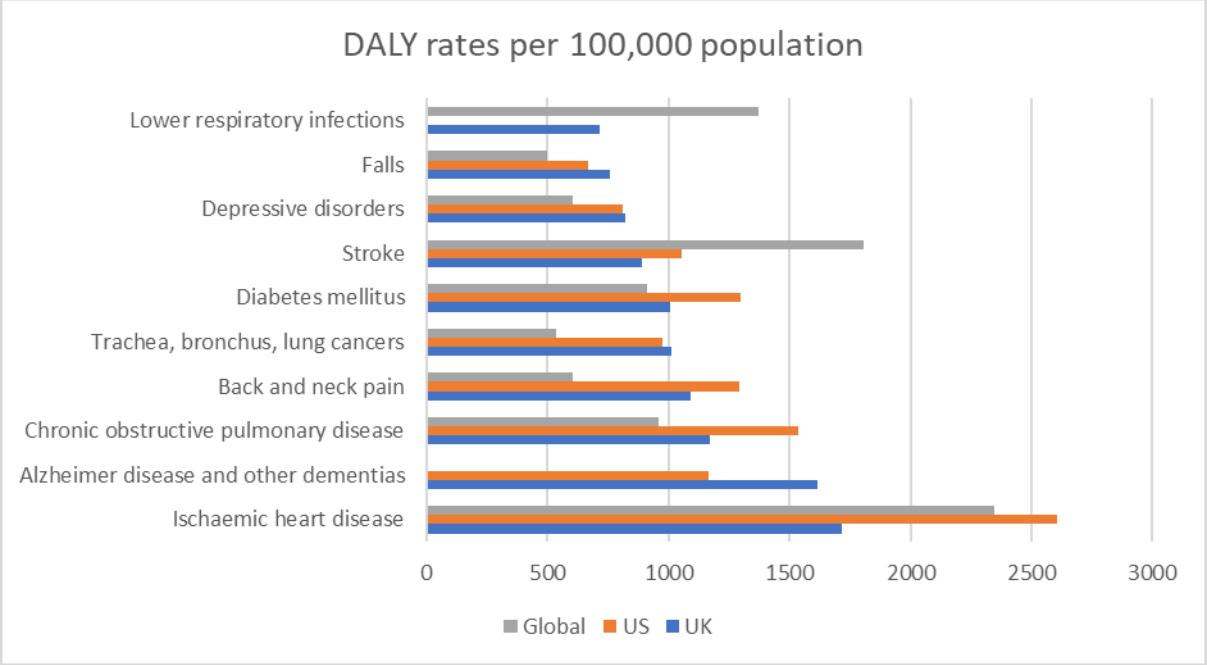

Table 15 – Disease burdens of different disease states across the Global, US, and UK

Burden/DALYs

Ischaemic heart disease, stroke, diabetes mellitus, chronic obstructive pulmonary disease (COPD), depressive disorders, falls, and back and neck pain are top 20 causes of DALYs across the UK, US, and globally. Lower respiratory infections are a major (top 20) concern across the UK and globally. Alzheimer's disease and other dementias appear to be more prominent in developed nations like the UK and the US.

Selecting disease states

Analysis led to five disease states as the leading conditions to focus on within the UK – with the two disease states selected being lung cancer and respiratory infections.

	Mortality	DALYs	Innovation potential
Lung cancer	High	High	High
Cardiovascular disease	High	High	Medium
Respiratory infections	High	High	High
Dementia	High	High	Low
COPD	High	High	Low

Table 16 – Analysis of disease states for prioritised focus

Lung cancer has the highest mortality rate of all cancers and will be used as a model for IVD solutions across all oncology areas. There is a limited scope for IVD innovations in cardiovascular disease, and there will be an overlap in IVD innovations across other disease states in which there are needs for molecular detection. Respiratory infections have an extremely high incidence rate and can be used as a model for all other types of infectious disease – with the need for detecting viruses, bacteria and fungi being useful across the board. Both dementia and COPD have high disease burden, but there is limited scope for innovations in diagnostic tests which require a physical biological sample. In general, technologies required for detection of pathogens and molecular entities will be common to all disease states and so using lung cancer and respiratory infections will be a useful focus to discover all the key technologies in the whole area of IVD.

Conclusions

Lung cancer and respiratory infections are the key disease states on which the technology-based opportunities can be identified. They will be used as models to identify the broader needs of the other disease states.

The focus on lung cancer and respiratory infections as the key disease states does not mean that the technology roadmap will not provide answers for other diseases. Technologies used in the selected diseases will be applicable across most other diseases. The selected disease states were used to search for technologies to build the roadmap, acting as proxies for the other disease states. This was validated by industry experts who know the IVD landscape around the other disease states.

Appendix C: The technology opportunities

Digital PCR (dPCR)

Strengths

dPCR has a number of specific advantages over standard qPCR. These include:

Highly accurate quantification of target DNA sequences

- Quantitative PCR (qPCR) can generate a Cycle Threshold (CT) count, but this is far less accurate than dPCR

Ability to detect very low frequency targets

- qPCR data tends to be dominated by the majority sequence at a particular point and struggles to detect lower frequency sequences

Lower sensitivity to inhibitors

- qPCR can have its efficiency significantly lowered by inhibitors such as heparin and haemoglobin but dPCR, due to its compartmentalisation and higher cycle count, is less sensitive to this

Single endpoint reading rather than once per cycle

- This simplifies the optical design.

Technical challenges

Compartmentalisation is the key to dPCR and is its primary challenge. The sample plus the reaction mix must be split across a large number (many thousands) of separate aliquots. Ways of doing this include microfluidic chips or water droplets formed in an oil matrix. These methods are expensive and require complex single-use cartridges and complex instruments. In addition, sophisticated optics are required to read the many separate reactions.

Currently available systems are expensive and have high disposable costs and consequently cannot be used in standard high throughput clinical labs or Point-of-care (POC) environments. Clinical medicine therefore rarely accesses the benefits that dPCR could deliver.

Feedback from clinicians

Lung cancer specialist: Next generation sequencing (NGS) generates excessive data, is time intensive and does not detect fusion genes; a rapid multiplex digital PCR that picks up fusion genes would be ideal.

Respiratory infection specialist: This would make a real impact on antimicrobial stewardship, enabling quantitative analysis, detection of antimicrobial resistance genes, detection and differentiation of pathogens.

Feedback from the industry

Benefits of digital PCR

"dPCR is halfway between sequencing and qPCR due to its ability to detect rare sequences – it can collect this data in a faster and cheaper way than sequencing. This would allow speeded up detection in diagnostics but also could help with other applications such as waste-water screening for, among other, Sars-CoV-2 sequences. Direct and accurate quantitation of viral load during treatment is another area where dPCR could be very useful. It also can detect foetal DNA sequences in maternal blood and so help with pre-natal screening and assessment."

"dPCR is more likely to be used in centralised large lab diagnostic centres rather than POC and clinics due to the higher complexity of its equipment and its more specialist applications. Currently dPCR is used in hospitals using reagents created specifically by the lab, i.e. "home-brew" or in a Lab-developed-Test (LDT)-style application which uses Research Use Only, and not IVD reagents. This internal use could stimulate interest in adding dPCR capability to the larger centralised testing instruments."

Challenges of digital PCR

"It is not a particularly difficult technical change to make dPCR part of the diagnostic mainstream – most challenges are around clinical acceptance and readiness to make use of accurate quantification."

Clinicians do not generally know how to make use of the accurate quantitation of bacterial and viral loads. It is uncertain whether they would pay for the additional benefits. Additionally, the biological relevance and arguments in terms of health economics are not certain for such accurate quantification."

dPCR cannot be carried out on existing platforms within laboratories, and so would make it necessary for the labs to purchase expensive new instruments. The current limited use of "home-brew" tests within laboratories may make companies unwilling to invest in the development of completely new instruments. The clinical demand would have to be demonstrated."

Sequencing

Strengths

There are several different DNA biomarker types that can be assessed: from minor differences in DNA building blocks, called Single Nucleotide Polymorphism (SNPs) to significant DNA rearrangements and deletions. Depending on the specific clinical application, either the whole genome, the exosome or specific individual genes can be sequenced.

Sequencing the host genome allows a highly detailed understanding of the individual's propensity for a wide variety of diseases - from heart disease to diabetes and cancer. It can be used to determine how patients metabolise different treatments and so help choose the optimal drug dosage. As part of a personalised medicine approach, it can also determine which of a series of therapies are most likely to be beneficial for a certain patient – for example EGFR gene sequencing can determine which inhibitor drugs should be used.

Sequencing is particularly useful for the identification of rare diseases which often have an identifiable genetic cause.

Challenges

While sequencing systems exist, they are not yet a major component of routine diagnostic procedure. This is for a variety of reasons around cost, throughput, and availability.

The leading DNA sequencing technology is commercialised by Illumina. The process involves a series of different steps (DNA isolation, library preparation, sequencing, and data analysis) which all use different and expensive separate instruments and require highly trained staff to operate. The current systems are not suitable for use in a traditional and more automated public health laboratory. In addition, the technique only reads a few hundred bases per reaction and consequently many DNA fragments must be read many times before a consensus sequence can be produced using complex software.

Feedback from clinicians

Lung cancer specialist: "NGS cannot identify fusion genes and provides a lot of data that many clinicians do not understand. Also, the NGS turn-around time is too long, and the cost is still on the higher side. Identification of oncogenic drivers and new mutations would have clinical applications in cancer."

Respiratory infection specialist: "Understanding the drug-or-antibiotic resistance pathogens and why certain therapies work on some patients and not on others has potential application in respiratory infections. However, sequencing turn-around-time needs to be a bit quicker and cost less."

Feedback from industry

Benefits of sequencing

"Sequencing can deliver personalisation and stratification (e.g. linkage to companion drugs), with broad applicability in earlier detection of both cancer and rare diseases. It will need to be properly integrated into the clinic and into healthcare to be successful."

"COVID-19 changed the mindset and now the average person understands basic concepts in diagnostics, such as lateral-flow and PCR, and the value they can bring. Sequencing will go through a similar process by lay people leading to a broad understanding and acceptance of its value."

"Sequencing is still not used routinely in central labs and may be an enabler for other advanced diagnostics such as digital PCR. It could help with quicker uptake of more incremental tests by helping refine the use of existing diagnostic tests and so bring a general change in diagnostics."

"Broad use of sequencing could also support a move for the development of expertise and collaboration between NHS and private companies to push quicker adoption of Artificial Intelligence/Machine Learning industry."

"The UK is a leader in sequencing and can help find new biomarkers for various diseases. The UK could discover valuable DNA-based IP and expedite the launch of new clinical markers – depending on sequence

universality, it could potentially be used globally. Sequencing adoption is likely to start with a small set of cancers and then grow to other diseases."

Challenges of sequencing

"Sequencing (e.g. Whole Genome Sequencing or Whole Exosome Sequencing) can potentially provide a huge amount of information relating to a person's biology. But this information must be clearly linked to unmet needs in diagnostics (and not just use of the technology for its own sake) otherwise it will not be adopted by the NHS. The analysis of all this data is difficult and requires AI/ML technologies for its interpretation in a useful timespan. The analysis must be presented in a form understandable by clinicians as they cannot be expected to interact with complex sequence building programmes. Much of the clinical workforce will need educating in sequencing and the benefits it can bring to clinical practice."

"One of the systemic challenges for the NHS is adopting new diagnostics, as there is a lack of clear access and reimbursement routes for extra costs in the standard hospital environment. It is not obvious who and which department funds these costs. The true clinical value of diagnostics is not recognised and appropriately funded, and its reimbursement is not value driven. There is no single central authority that drives diagnostic uptake in the NHS and the different trusts operate in different ways."

"Another challenge is that integrating sequencing with existing healthcare solutions and approaches is not easy. As needs are not currently linked to benefits then a 'chicken and egg' problem develops as to which comes first. It may be that private healthcare uses sequencing first, as it can afford costly tests that the NHS cannot."

"Overall costs are currently too high for sequencing and will need to be reduced for implementation within clinical practice. The NHS could contribute and pay a share of the costs for a test, within its individual trusts, to help bring costly tests into clinic. Another challenge is that extra diagnostic testing will find diseases that need additional funding to manage or treat, which may not be appropriate, available, or affordable."

"There are significant security, ethical, and regulatory issues. These are linked to the control, movement, and visibility of data. For example, data transmission between different countries is difficult due to private cloud companies and this has been made worse by Brexit – as well as the erosion of the available talent pool in the UK. Other ethical issues exist, e.g. the implications of a genetic disease being diagnosed in one member of the family and whether this information should be communicated to the other members. Patients may fear and refuse sequencing due to these issues and also to the potential impact on the cost and availability of medical insurance."

"The UK IVD industry has several challenges to sell products in the sequencing space. To sell in the UK, it needs to work with the NHS – that is difficult due to its fragmented nature. Even after Accelerated Access Collaborative (AAC) / NICE approval, it is unclear if uptake will really happen in the NHS. New care pathways would have to be developed to make full use of sequencing which the NHS would find very challenging. Regardless of this, to make a profit from its R&D investment, sequencing products need to be competitive enough to sell to global markets. Consequently, NHS adoption is only a small part of the problem."

"There is limited manufacturing infrastructure for IVDs in the UK as the standard model is that IP is created in small companies, demonstrated technically, and then sold to the big (foreign) IVD companies for commercialisation. Part of the reason for this is due to a lack of clear long-term commercialisation routes

which makes a slow ROI after initial launch. Government support is needed in the form of tax benefits to act as suitable incentives for commercialisation and UK entrepreneurship to help prevent this."

Cell-free nucleic acids (cf-NA)

Strengths

The cf-NA has several advantages over tissue biopsy and holds promise for the less-invasive detection of tissue-specific pathologies with a range of clinical applications:

- The sampling procedure is easy, less invasive, more repeatable, cost-effective and can detect cancer early
- cf-NA can deliver information about the whole tumour and has the potential to provide information on its origin
- Suitable for diagnosis as well as treatment monitoring and disease progression
- Recent advances in PCR, NGS and microfluidics have enabled the use of circulating nucleic acids in diagnostics. Reverse transcriptase qPCR is the most established analysis method due to the wide availability of standard systems, sensitivity, specificity, and reproducibility.

Challenges

Although there is a lot of interest in cf-NA detection in cancer and other diseases, the technology is still in its initial phase and has several challenges.

- There is a lack of reliable biomarkers for diagnosis and treatment monitoring and a lack of standard protocols.
- Detection and quantification of cf-NA is difficult due to its very low concentration, its short molecular length and the presence of normal DNA which makes detection of cf-NA much more difficult.
- Next-generation sequencing is widely used for cf-NA profiling. However, it has limitations due to its need for cf-NA enrichment, its higher error rates of sequencing, its high cost per analysis, and it requires significant amount of expert skills for library preparation and bioinformatic analysis.

Feedback from clinicians

Lung cancer specialist: "Fundamental science is obviously here. Its application to monitor oncogenic drivers, methylation profiling and tiny tumours which cannot be detected by CT is the next big thing in early cancer detection."

Respiratory infection specialist: "This is good for cancer and cardiovascular diseases. Monitoring lung damage through cf-NA would be good in respiratory practice."

Feedback from industry

Benefits

"Cell-free nucleic acid analysis is a minimally invasive way to replace unpleasant and risky biopsies, decrease exposure to X-rays and to diagnose disease significantly earlier. It helps mitigate some of the impact of a shortage of radiologists and could even have lower costs across-the-board."

"It could also be used for pre-symptomatic screening for cancer and, post detection, at multiple points in the treatment process to check on its efficacy. Multiple sampling events are very possible with the theoretical possibility of using it daily during early treatment to get rapid feedback."

"Cell-free nucleic acid analysis could enable home-based sample collection and lab-in-an-envelope style analysis. There is the potential to repurpose equipment and infrastructure, such as the large Rosalind Franklin lab purchased during the COVID-19 pandemic, to create new cancer testing centres using cell-free nucleic acids."

Challenges

"The analysis of cell-free nucleic acid is challenging as the length of the DNA molecules is short and the yield of cell-free DNA is very low. Only a small amount of circulating nucleic acids can be captured and analysed. New and better purification methods need to be developed. Complex computation analysis is also required to convert the output data into a meaningful form."

"The discovery of new biomarkers of cell-free nucleic acid is also a challenge. Apart from the technical challenges, it is not easy to get the clinical samples required to do the necessary clinical research."

"It is not yet clear which are the most clinically and economically beneficial applications for the technology. Screening of high-risk populations is potentially its largest market, but its prognostic and predictive power is unclear. In these markets, it may be too expensive and provide insufficient benefits to meet the costs."
"The reimbursement potential is unclear as it is not known what differential it will offer over existing technology. It will be a real challenge if its cost effectiveness can only be shown over the patient lifespan. This is in context that therapy receives the lion's share of healthcare funding, and without these links, it becomes difficult to pay for the tests."

"The complex AI/algorithms used within these tests provide different decisions to those that would be predicted by a clinician today through their experience and judgement. That difference is not sufficiently understood today to re-align the algorithms to the decisions that clinicians would make."

"The clinical utility provided by tests which use circulating nucleic acids must be better defined, along with the data requirements required for their progression through regulation and adoption. The new clinical pathways are not clear, and neither is who will define them."

"If a new test was developed, such as screening for diseases at an earlier stage, with both high-volumes and low-costs, the UK may not be able to afford them even if there is a clear long-term benefit. The test could be developed in the UK, but there is an assumption therefore that it would be used in the UK. Overall, the statistics for UK adoption of new diagnostic technology is very poor as the NHS is a tough environment for such tests to be adopted. The NHS has strong preferences for not changing its clinical pathways, which

make it challenging for market entry of truly novel tests. In addition, it is difficult to form collaborations within the NHS to acquire samples with supporting data and run clinical trials."

"While the FDA is not an easy hurdle, the US does define what is required in a clearer way than the UK. These new tests are likely to have to pass tougher regulation that current tests, with a combined discussion from makers, regulators, healthcare provider and users needed to deploy them successfully."

"IVD companies need to understand the complex regulatory, clinical, and economic aspects of the new tests but access to high quality advice is limited. The companies need a clear route to market, especially if it is within the NHS. Other territories, such as the US, have commercially accessible routes such as their form of Lab-developed tests (LDTs) which may well be a better option for UK companies."

"Market dominance of many of the incumbent major players makes it difficult for new players to emerge, even if they are developing better sequencing technologies or trying to launch a new test."

Digital biomarkers

Strengths

Physicians cannot see their patients often and it is not possible for patients to keep track of their symptoms and daily activities (e.g. sleep, exercise, and diet) which leads to imperfect diagnosis and treatment. Digital biomarkers can provide a more comprehensive picture of a patient's day-to-day activities and allow doctors to measure the changes accurately. This could potentially lead to better diagnosis, slowing down the disease progression or even preventing or reversing the disease.

Additionally, it could minimise the spending on unnecessary health services, promote patient independence and improve outcomes.

Digital biomarkers can provide continuous measurement of different parameters and produce qualitative and quantitative data in an easier and cost-effective manner.

Advances in digital wearable devices and smartphone apps can track clinically relevant digital biomarkers that could accelerate clinical developments (e.g. by selection of relevant patients for clinical trials) making them more precise and most cost efficient.

Challenges

- There is a lack of data standardisation across their source, format, and scale. Significant quantities of data are generated but there are few guidelines on how to store the data.
- Identification of the most relevant data for analysis, the method of analysis, and their baseline is still not obvious. There are various proprietary processes available from different vendors.
- Regulatory standards are way behind the rapid innovations happening in the digital space and are always changing and complex. For example, a digital healthcare device's usage is what determines its regulation status, not what it is and what it can do. Regulatory guidelines on data privacy and data ownership are not fully developed, continuously change, and are inconsistent between different countries.

- Many digital footprints can lead to data protection/data privacy problems and possibly manipulation of human behaviour by interested commercial/political influencers.
- Disparities in the output of technologies can cause problems, for example when there is a difference between data collected by devices and what is reported by the patient.

Feedback from clinicians

Lung cancer specialist: "This is easy in neurology, cognitive, cardiovascular disease, and mobility-related conditions and slowly progressing in cancer."

Respiratory infection specialist: "This is a crazy area with many options but there is no standardisation; data ownership and regulation are big challenges ahead. Clinicians need the power to align the data captured through digital healthcare technologies, apps, and wearables, into patient medical recording systems."

Feedback from industry

Benefits of digital biomarkers

"Its light touch and non-invasive nature make it suitable for detecting/screening very early stages of disease, medical compliance, and effectiveness tracking of post-medical intervention (such as prescribed exercise plans, pill taking etc.)."

"It is naturally suited to continuous monitoring and with an intervention-based feedback loop could help improve wellbeing through life-style monitoring. Continuous monitoring could also help to correlate data to specific lifestyle events and hence add more precision to its analysis and predictive powers."

"It can deliver very personalised data and this could be shared with the patient to increase its visibility – this may help with ensuring compliance to medication or to a healthy lifestyle."

"If used with cost-effective devices (e.g. apps) and infrastructure (the existing mobile phone network) it could perform very large-scale data capture and help lead to the democratisation of healthcare – i.e. everyone has access to its benefits."

Challenges of digital biomarkers

"Assessing digital biomarkers could generate huge volumes of data that are very difficult to review, analyse, and make sense of. The data must be interrogated and calibrated in such a way that allows actionable steps to be interpreted. If not correctly calibrated to have the necessary sensitivity and specificity, it could significantly increase costs by sending too many people for unnecessary diagnoses. At present, it is not clear what value digital biomarkers can deliver and where best it should be used on the clinical pathway."

"There are challenges in data privacy, especially if data needs to cross borders and be used across the world. Different countries have different regulations, costs for access, and privacy laws."

"It is not clear how companies could get competitive benefits especially around IP. A cross-industry strategy is likely to be required between consumer technology companies, health tech companies, and government, to generate and utilise the necessary infrastructure and allow the connection/cross fertilisation of digital data with clinical data."

"Digital biomarkers will have to be clinically validated and then clinicians (and patients) will need to be educated about how they should be used and their limitations."

"Leading academic institutions in the area are the University of Strathclyde, University of Southampton, University of St Andrews, St Mary's College (University of London), and Imperial College London."

Proteomics

Strengths

Changes in disease state are not always expressed in the DNA sequence (due to the difference between the fixed DNA-based genotype and the variable protein-based phenotype), so specific sets of proteins can give more accurate physiological information on the disease processes.

The field of proteomics has benefited from new technologies in peptide/protein separation, mass spectrometry analysis, quantitative protein analysis, statistical methods, and databases to enable the simultaneous analysis of thousands of proteins in a single biological sample.

It has been recently found that many cancers show modified protein handling processes and hence have altered protein patterns compared to healthy cells. In addition, peptides have been discovered that have been expressed from DNA sequences previously considered to be non-coding regions. These findings combined with new technical advances potentially allow a new level of clinical information to be used.

Challenges

While mass spectrometry-based proteomics is a powerful and universal method for the global measurement of proteins, it requires expensive equipment and complex time-consuming protocols. Also, research has not yet been able to identify specific proteomic signatures that can be used as clinical biomarkers.

Even if proteomic biomarker signatures are found, before they can be used in routine clinical assessment, more limited subsets of protein biomarkers must be identified that require simpler and lower cost equipment. These smaller sets of biomarkers are yet to be identified. Clinical utilisation will have to wait until practicable small protein subsets are identified.

Feedback from clinicians

Lung cancer specialist: "Too much data generated by omics inhibits the desire to get information. The specific protein signatures of early-stage cancer would be better applicable for early diagnosis. Combining protein signatures with liquid biopsy and ML/AI can better predict the risk of cancer. A simple mass spectrometry technique for protein analysis might be useful for clinical applications."

Respiratory infection specialist: "It would be interesting to see the change in inflammatory proteins to guide the treatment of infections, cancer, and cardiovascular diseases. However, nothing significant was seen in diagnostics despite the established technology."

Feedback from industry

Benefits of proteomics

"Proteomics could help with the early diagnosis of cancer and selection of therapy in the form of novel companion diagnostic tests. It acts as an additional level of information to that provided by nucleic acids. Due to its potential to follow the protein pathways and hence the impact of disease, it could also help stratify patients and link them to specific treatments."

"An incremental (i.e. achievable) path could be created from the current state to a new future state by replacing single protein diagnostics by more multiplexed proteins – replicating the pathway of single plex PCR to multiplex PCR."

"It has a natural linkage with sequencing and could share common builds/usage and infrastructure with it. Unlike sequencing, proteomics is early in its development phase as biomarker patterns have not been fully defined yet. Consequently, the UK can retain maximum IP and its value in this area."

Challenges of proteomics

"The cost of bringing proteomics into routine clinical use could be prohibitive. At this moment, its re-imbursement mechanisms and its place in the clinical pathway are unclear. Despite being an area of investigation for ten years, it is at an early stage without properly defined biomarkers. It needs definitive and actionable biomarkers to be of use – with validation needing further investment and development. There may also be alternative solutions to the same clinical needs which have better cost-benefit profiles. Even then, for developing and validating tests based on proteomics, it is difficult for companies to gain access to samples."

"The UK does have some weaknesses in investment, supply chain infrastructure, and delivery due to limited funding. This means that there is a danger that the UK's strong IP in this space could be sold at an early stage, as seen in other areas of diagnostics. To avoid this, the UK must develop the manufacturing capabilities at-scale, so that it can really undertake end-to-end development."

Combined biomarkers

Strengths

For complex multifactorial diseases, combining the sensitivity and specificity of separate tests may enable better clinical decision making. Diagnosis done through multiple combined biomarkers could have better sensitivity and specificity; it could detect diseases at early stages, differentiate between disease subtypes and patients could therefore benefit from early treatment.

Diagnosis based on combined biomarkers could possibly answer several questions such as better diagnosis, of patients with comorbidities, estimating the impact of a drug on a particular disease, following disease progression, and potentially identify drug targets.

Progress in multi-biomarker diagnostic tests could potentially expedite the translation of omics technologies into clinical practice, which can further help identify additional disease-specific biomarkers.

Challenges

Several combined biomarker sets have been discovered but the role of each individual biomarker is not always well validated. Some studies have shown promising results. However, many studies lack appropriate sample sizes. Therefore, extensive validation is needed to train multiple biomarker-based diagnostic tests, integrate with omics technologies, standardise assays and compare to existing tests to improve performance and their acceptability.

Machine Learning (ML) is frequently used with multiple biomarkers to predict the outcome; however, ML-based molecular diagnostic tests lack standardisation, a reference for comparison, and clinical guidelines as it is a relatively new field and needs additional capabilities in deep learning.

Analysis of the tests becomes expensive with many biomarkers. The reimbursement pathway of ML-based molecular diagnostic tests is therefore challenging.

Feedback from clinicians

Lung cancer specialist: "Combining various biomarkers obtained from blood, lifestyle (such as smoking in lung cancer), clinical symptoms, and AI/ML to get a prediction score is something many companies are developing; however, the challenges are with the sensitivity and specificity. Ideally, a sensitivity and specificity of >85% is considered good. The real impact of combined biomarkers would be in predicting the early-stage cancer population."

Respiratory infection specialist: "Collection of information from all possible diagnostics and processes into computing power is absolutely the future. This will make doctors' lives easier, but the challenge is designing algorithms that think like a doctor."

Feedback from industry

Benefits of combined biomarkers

"The concept of combined biomarkers has, at its core, a cross-pollination between a range of biological-related disciplines. This will increase patient benefits through its multi-purpose applicability including aetiology, prognosis, risk assessment, diagnosis, and treatment, and has broad applications, such as cardiology oncology, treatment strategies, and anti-microbial resistance. It has the potential to increase the speed of detection through its combinatorial approach using new and existing biomarkers."

"Combined biomarkers will build a complete health picture to involve both diseases and outcomes. This will allow real-time, automated patient monitoring and help in testing for rare diseases."

"There is the potential to use the NHS as a test bed and for the UK to take a lead in this area – e.g. building on the widespread use of the NHS app during COVID-19 – especially as data privacy is more advanced in the UK, e.g. the General Data Protection Regulation (GDPR)."

"It could improve lifestyle changes to keep healthy with potential empowerment of people and patients leading to better and possibly cheaper outcomes over the long term. By tapping into decentralised healthcare, it could bring in millennials, GenY, and GenZ since they are often not closely linked into the current healthcare system."

Challenges of combined biomarkers

"This is a highly complex area and involves a collision of worlds that are often siloed – big IT, government, and users. There will be many issues with trust – who owns and has access to the data."

"It requires very significant development and infrastructure and must be carefully integrated into clinical practice so that it can interact with multiple different parts of the patient's journey."

"It will require continual updating to future proof the IT systems and so they do not get left behind by technological development – and yet we do not yet know the full value of the benefits it could deliver and whether its full complexity is necessary. There are concerns around regulation, data security, data ownership, data transfer, and privacy concerns – with a potential for impact on insurance etc. In this context, the UK industry has limited experience."

"Diagnostic data and lifestyle data will be different in structure and content, are unlikely to have the same issues as each other, which means that linking them together may be difficult. This will make the development and validation of precise algorithms a challenge, requiring complex research and prolonged testing. The "behind the scenes" IT tech does not really exist yet and will require significant investment."

"Reimbursement is a significant challenge for this area – demonstrating the value of novel solutions which use combined biomarkers and their cost-effectiveness with NICE. Clinicians will need significant education about the new capabilities as otherwise there will not be much acceptance for the new combined approach."

"Unless all aspects are government funded (e.g. devices etc.) then it will exacerbate access inequalities due to wealth and education. Even if fully funded the Government may need to change its policy from an opt-in approach to an opt-out to decrease the impact on inequality. Once opted in, there may be consumer/patient anxiety as they will be constantly monitored and under-diagnosed."

Exosomes

Strengths

Exosomes are now considered to have multiple roles in lung cancer, including carcinogenesis, progression, cell proliferation, metastasis. Exosomes affect angiogenesis, modulate antitumour immune responses, and regulate drug resistance in lung cancer therapy.

They achieve these multiple functions by delivering multiple and diverse types of nucleic acid into their target cells – the long non-coding RNA is one of the more important components.

Due to their significant role in lung cancer formation and progression, there is much interest in using them as biomarkers and diagnostics across the range of different disease stages.

Challenges

There are several challenges that prevent routine analysis of exosomes.

Firstly, the field of exosomes is very much in R&D and it is unclear the clinical significance associated with different exosome populations present in a particular sample.

There are no effective ways of isolating and purifying all the exosomes in a sample. Several different methods exist but they are labour-intensive and tend to collect different sub-populations of exosomes making it very difficult to compare between them.

Since exosomes contain several different molecular types, it is difficult to analyse them all, as each method tends to destroy the other types, e.g. nucleic acid purification techniques inactivate proteins.

Due to purification challenges, several subsequent procedures (full nucleic acid purification, library preparation, and sequencing) are required to determine what sequences are present. These are time-consuming and expensive procedures and very different to what is needed in high throughput diagnostic labs.

Feedback from clinicians

Lung cancer specialist: "There has been a lot of research, but I am not sure if exosomes are reliable enough, like cf-DNA and circulating-tumour cells, until fundamental research is done."

Respiratory infection specialist: "This is a frontier in science with potential applications in ageing and cancer but too early for commercialisation."

Feedback from industry

Benefits of exosomes

"Exosomes offer the potential for less invasive assessment of disease in specific organs and tissues. Since many exosomes are released continuously, multiple repeat testing is possible during treatment allowing its success to be monitored. It could be also used for population screening to detect disease prior to symptoms."

"Due to its internal constituents of RNA, proteins and lipids, exosomes represent a relatively simple first step for multi-omics analysis (i.e. the assessment of several molecular types simultaneously)."

Challenges of exosomes

"It is not known if exosome analysis will be a cost-effective way of assessing disease and there may be cheaper ways to collect the diagnostic information that it can deliver."

"Current purification methods are expensive, have long hands-on time (over three hours), longer overall time (13-14 hours), and do not scale well. Part of the reason for this is that the current purification methods are not sensitive enough – many exosomes are not captured."

"The necessary biomarkers to make clinical use of exosomes have not yet been discovered and validated. Investment is needed to get the large amount of data required to prove if this is of significant utility – a classic "chicken and egg" situation. There is clinical interest but no real demand as utility has not been proved."

Single cell analysis

Strengths

Single cell analysis allows measurement of the cell-to-cell variation which occurs during disease.

It prevents the signals from rare diseased cells being masked by the larger population of healthy cells. For example, the tumour micro-environment contains multiple interactions between tumour cells and neighbouring stromal cells, including fibroblasts and immune cells, which have different implications in pathogenic conditions. These would be missed if average values were taken of all the cells. Understanding cell-to-cell variation at the level of a single cell will unlock new potential diagnostic tests.

Challenges

During cell isolation, the spatial context of its local environment that can define a cell's activity is lost – and this context helps understand how they interact with each other and hence their role in health and disease. The limited amount of starting material, e.g. mRNA, can lead to the creation of misleading errors when it undergoes testing by PCR. Other distortions can be created due to differences in the capture efficiency of different molecules.

Different isolation methods vary in their ability to keep the cell alive without affecting its characteristics.

Single cell analysis is generating new data science challenges when linking research hypotheses to vast amounts of data. The scale of data comes from new techniques that allow thousands of cells to be analysed in each experiment.

Feedback from clinicians

Lung cancer specialist: "This is more popular in academic settings rather than clinical ones. The heterogeneous nature of tumours limits the single cell approach in cancer; however, a cognitive approach is needed when you pick cells as it would require several cells from different tumour sites."

Respiratory infection specialist: "It would be more interesting to detect hard-to-find bugs and drug-resistant markers quicker than culturing."

Feedback from industry

Benefits of single cell analysis

"Single cell genomics enables precision medicine for targeted treatments. It minimises the requirements for tissue biopsies and can be combined with imaging to monitor and inform treatment through detecting what works. It could also allow spatial information to be collected on the 3D nature of the disease."

"If used for bacterial infections, it could allow rapid detection of anti-microbial resistance and targeted treatment – this could be delivered far faster than conventional culturing approaches."

Challenges of single cell analysis

"It will be very difficult to get a return on investment within five years as this is a long-term proposal. This is due to many issues including: lack of suitable instrumentation and skilled people, unclear clinical/economic value, unclear regulatory path, and uncertainty over developing the appropriate new clinical pathway."

"It is much more likely to be used as a companion diagnostic as the major benefit appears to be around the selection of therapy and monitoring its effectiveness. Consequently, it will be necessary to partner with a pharma company and define the test's value with them. Developing the test outside of the treatment will be very risky without a certain knowledge that the use of the diagnostic test improves clinical outcomes."

"Developments around single cell analysis are likely to be pharma-led projects, as the cost and the benefit is tied to the associated drug. Partnering with pharmaceutical companies is not necessarily easy as there

can be disagreements as to the costs of developing new IVDs and determining a fair division of the value created. Consequently, the development of these types of tests tends to be driven by the pharmaceutical company."

"There is significant regulatory difficulty: EU approval has clear regulatory development milestones but also has long and undefined wait times; and the UK regulatory milestones are not well understood (and probably not clearly defined). The companies launching the first products would probably have to work closely with the regulators to understand, develop and implement the necessary regulatory framework. It is uncertain whether the UK will follow the EU's regulatory approach or the US's. Recent changes in moving from IVDD to IVDR has meant that the necessary Notified Body infrastructure is not set up in the UK and it may take a long time for it to become easy to access. Regulatory assistance is very important for these complex technologies."

"There are also technical challenges to implementing this approach as complex microfluidic and cell manipulation is required."

Metabolomics

Strengths

Metabolites reflect the activity of proteins and serve as signalling molecules for processes that include gene and protein regulation. As such, the added value of metabolomics is that it reflects, complements, and informs data acquired by other biological analysis such as genetic and proteomic. Because metabolic profiles change rapidly with the biologic state, metabolomics permits unique insight into both the pathogenesis of disease and drug response (pharmacometabolomic), as well as often unapparent changes in phenotype.
The fundamental premise in metabolomics is that changes, whether physiological or pathological, cause alterations of the metabolome that are detected as variations in metabolite concentrations. It therefore represents an additional class of information that clinicians can use to make better treatment decisions.

Challenges

Individual metabolites are used routinely in clinical chemistry. However, more work is needed to confirm and validate links between metabolic changes, clinical phenotypes, and biological processes to further understand disease pathogenesis, and ultimately to drive drug discovery and achieve precision medicine.

No one platform captures the entire metabolome, there are several analytical platforms that can be used, each of which has its own advantages and disadvantages. Metabolite identification is particularly challenging for lipids, as large numbers of lipids have very similar or identical analytical signatures.

Feedback from clinicians

Lung cancer specialist: "This is another exciting area but more complex than anything else. Defining metabolic signatures of cancer will be hard due to the different half-life periods of metabolites. I don't know if it is ready for wider clinical applications."

Respiratory infection specialist: "Metabolic analysis of body secretions such as sweat is exciting. Metabolites of healthy vs diseased conditions can help monitor treatment, however it feels at the pre-diagnostic stage. Refining the technology for clinical applications would be challenging and need a huge investment."

Feedback from industry

Benefits of metabolomics

"Metabolomics has the potential for broad spectrum wellness testing. It has the potential to discover and use many new biomarkers. It will require much data capture and analysis, and the UK has a chance to lead in the creation and use of a big data new database."

"Metabolomics has the potential to inform diet and lifestyle choices for the well population and there is a good linkage with the consumer market."

"Continuous long-term monitoring is the most likely way that metabolomics could prove its utility."

Challenges of metabolomics

"Metabolomics is challenging since it is more of an approach rather than a defined activity. It uses several simple chemicals that are already studied and adds a significant number of new ones in a highly multiplexed way. The utility of the high-level multiplex data has not yet been proved; it needs significant technical development in biomarker discovery. As these have not yet been discovered then there is no defined benefit to its use and no true developed clinical or business case for it to be adopted."

"If biomarkers that deliver value can be found, then it will require extensive data to be collected and analysed, and so they share many of the problems faced by proteomics and digital biomarkers. It is currently a research application and is a long way out from technology readiness."

Appendix D: Technology developments

New materials

Atomic-layer deposition. This has the potential to make a variety of new materials with targeted properties. The challenge will be to create a reproducible layer with no drift at commercial scale, in a suitable timescale as the process is very slow. Currently, it is used for nano coatings and thin films, especially in displays, but its mass scale usage will increase. Time for development is expected to be medium-term, but long-term for its use in diagnostics.
Functionalised chips as new materials. Chips can be functionalised to create new surface properties, for example the use of micro scale localised heaters on a chip to synthesise specific long DNA sequences.
Graphene. Graphene will find niche applications but is unlikely to be widely used in these opportunities. A new manufacturing infrastructure for graphene has to be established which will take time to set-up. Additionally, it will need to demonstrate its utility over and above current complementary metal-oxide-semiconductor (CMOS) and micro electro-mechanical system (MEMS) electronics and sensors.

New enzymes

New antibody forms. This includes the development of novel binding proteins which can act as "mini-antibodies" with better performance, usability, and lower costs than existing antibodies.
Aptamers. These are short oligonucleotide sequences which fold into architectures capable of binding proteins and catalysing enzymatic reactions.
Advanced cell-free expression systems. These will remove the need for use of whole cells for production of biomolecules. This will enable faster production and easier fermentation processes, with the potential for continuous production. Such developments are more likely to be long-term.
Long length DNA synthesis. Long lengths of nucleic acid will be successfully and reliably synthesised using new manufacturing methods. Base pair lengths of DNA or RNA with 2000 to 3000 base pairs will allow the production of full enzymes directly from in-silico modelling in a single step when linked to cell-free expression systems. These developments are relatively short-term.
Targeted protein evolution. Guided evolution processes will enable the development of proteins with novel functionalities, with much greater success than the current random evolution approach. This is achieved by iterative rounds of mutagenesis on a gene to create variants, selection of the variants which best meet the desired functionalities and amplification to create a gene template to feed back into the process. This can be linked to the use of new rapid sensing methods (e.g. electrochemical or optical sensing methods) to assess activity of enzymes and improve the speed of the evolutionary performance.
In silico modelling. In silico modelling of protein function combined with the use of clustered regularly interspaced short palindromic repeats (CRISPR) technology to create the desired DNA or protein molecules.
Nanozymes. These are nanomaterials with enzyme-like properties, which can address the stability issues, high-costs, and storage problems with conventional biological enzymes. They may also have enhanced catalytic capabilities and more scalable production processes. They have potential uses in diagnostic chips, sensors, and assays. Additional properties could be physico/chemical, such as thermal, paramagnetic and fluorescence, adding another layer of key functions compared to enzymes.

Phage-based detection. Bacteriophages are viruses which specially infect and multiply within specific bacterial hosts. These properties could be used in future detection systems for bacteria, offering specificity and lower costs.

New optics

Computational imaging. Use of computational reconstruction methods such as Fourier ptychography. This involves taking multiple different images from different coherent illumination angles, using sophisticated software to combine them and produce a higher resolution image than the lens would normally be capable of achieving. This approach is now feasible due to the faster processing chips that are available. It allows a 5x objective lens to generate images that would normally require a 50x lens. The principle is that by using a slightly longer imaging time (e.g. capturing multiple images) cheaper optics can produce better results. Diagnostic companies in the US and in Israel are using this already as it gives a cheap solution to optics. This is available in the short term. The challenges are that there are no UK companies doing this yet and that very specific expertise is required.
Digital lens. Use of new lenses that are designed to integrate with digital systems rather than the human eye. Many of the costs of current lenses is from the correction for foibles/errors that represent limitations of human vision. Lenses are now being designed for digital systems that are cheaper to produce. These developments are medium term, but the challenge is that the UK has limited expertise in this area.
Multi-parameter images. Artificial colouring on images to add additional information. False colour can be added to black and white images to allow representation of additional parameters – like James Webb's telescope use of false colour for its Jupiter images. Additional chemical-based information can be added, replacing the information currently collected by chemical dyes. The new technique presents better images than those produced using chemical dyes. There is limited waste and no staining errors. This would be medium-term development.
Surface-based photonics. These are lensless photo chips that record image data directly onto their surface. They are based on wafer-scale integration of the optics on a chip (e.g. photonic integrated circuits). The pixels are getting smaller and are now at 400-500nm. Not much more advance will be required to allow lensless single molecule direct imaging. These new CMOS chips are much better than charge-coupled devices (CCDs) as they need no filters and record photons pixel by pixel without scanning. This is medium to long term. The challenge is that this is not ready yet and diagnostics will have to wait until the electronics industry achieves this at a realistic cost.
New LEDs. Light-emitting diodes (LEDs) are being produced that are cheaper, stronger, and better than standard LEDs. Multiple tailored wavelengths and pre-mounted LEDs are now already available at much lower costs. The UK has expertise in these LEDs, such as gallium arsenide in academic labs, but would have to support these developments through additional funding and investment in enabling technologies. These LEDs can replace lasers in many applications. Japanese optical and imaging companies are currently leading developments in this area.
Modular optics. Modular microscope optics are already available for use in other applications. Modular "bolt-in" systems for diagnostic applications would allow faster and cheaper development processes for new systems. The challenge is that the market size is not sufficient to enable economies of scale in production of bespoke solutions, so restrictions may be to adopt and adapt currently available solutions on the market.
Vertical-cavity surface-emitting lasers. VCSELs and other solid state laser technologies are improving in performance, while becoming less expensive. They are laser diodes, with laser beam emissions which are

perpendicular to their top surface, which leads to them being low cost and high-performance light sources. Timescale for developments will be medium term, at between two to five years.
Single pixel detectors. These produce high-quality images using devices with a single point detector and spatially structured illumination. They may offer improved detection efficiency, lower noise, and higher-time resolutions. Alternatives such as Gallium-Arsenide based detectors of mid-IR imaging are extremely expensive. The timescale is more medium term, between two to five years.
Plastic optics. Switching from glass to plastic materials for optical components, will save costs and weight. These are short-term developments, which require one to two years.
3D printed micro-optics. Such optics can be integrated into items such as microfluidic chips using 3D printing. 3D printing of micro-optics is reasonably well established, but it has not yet been applied to IVDs, and to microfluidic diagnostics. With correctly designed optics, a microfluidic chip could be placed into a reader that contains the light source and detector. The chip would contain all the optics, making the whole system small and portable. Key challenges are designing the overall system so that the chip is always located in the right position to obtain the reading. This will require some high precision engineering (both optical and mechanical). Its development would be more medium term (two to five years).

New microfluidics

Flexible substrates for fluidics. These will have inbuilt and integrated electrodes, enabling very low-cost health monitoring systems like those available for blood glucose analysis. The flexible substrate will be formed from electro polymers which carry current and can be also functionalised. Several polymers might be involved to achieve desired functionalities, as they can be co-melded. The device will comprise a very thin skin disposable patches with a hard cover, therefore serving as signal acquisition and communication/connection device. They can be built into a variety of devices, such as smart watches that can sense simple chemicals from sweat – close to metabolomics. These are medium to long-term developments.
Integrated electrodes. The ability to integrate electrodes into microfluidics will enable diagnostic devices with high sensitivities (limit of detection), high throughput capabilities and label-free detection. Standardised manufacturing methods will offer ease of design, high reliability and lower overall costs for development and volume manufacture. This technology will offer next-generation diagnostics with higher performance characteristics suitable for volume manufacture and overall lower costs for both development and build of materials (BoM). In contrast, today's technologies are based on hand assembly of inserts performing detection (typically functionalised nitrocellulose membranes). In the long term microfluidic chips will be fully plastic. But in the short term, they will be a hybrid combining different materials. Time for development ranges from short term to long term.
Functionalised microfluidics. These are microfluidic devices with a detection mechanism that has high specificity and selectivity built directly into the components. It requires reliable, repeatable, and localised functionalisation of micro-injection moulded polymers. Ultimately, manufacturing costs may be reduced even further if surface treatment and functionalisation become a post-processing step of the micro-injection moulding manufacturing process. Today, there are technologies available that offer low temperature bonding of micro-injection moulded flow cells on functionalised/treated glass substrate without affecting the surface chemistry of the glass. The technology is based on high resolution and precision 3D printing of epoxy resin. It may become an enabling technological advancement, which solves the current drawbacks of thermal/chemical bonding processes. Chemical functionisation of the electro-polymers is the easiest aspect to implement, but later developments

will have more complex biological sensing capability. This is a medium to long-term development space.
Single cell handling and analysis. Microfluidic devices which can encapsulate, handle, and analyse single cells in a high-throughput way are close to commercialisation. Label-free cell separation and sorting will broaden further the range of applications possible. These technologies are based on microfluidic methods (e.g. inertial microfluidics) rather than conventional binding methods, based on antibodies or purification media. They can replace micropillar-based technologies which require multiple and precisely controlled flow sources. Of the many detection methods for these technologies, optical detection is the most feasible available technology. There is the additional potential to integrate electrodes and use electrical detection (e.g. impedance measurements) instead of optical detection, resulting in instrument simplicity, mobility, and reliability.
New pumping and valving methods. Micro pumps do currently exist, but they are expensive. Currently, piezo-electric elements are used because of the high pressure needed due to the length of the microchannels. They function by pump strokes but consequently they result in pulsatile flow that compromises device performance. Consequently, pressure controllers are used today with a pneumatic drive that have much larger footprints and cost. There is therefore still an unmet need in the IVD market for low cost (single use/disposable) micropumps. MEMS-based technologies (such as phase change materials) may offer novel and enabling pumping/valving solutions. It would allow the monolithic implementation of actuation mechanism, reducing footprint, cost, and enhancing integration ability while eliminating required interfacing and thus reducing further dead volume. This is considered a medium-term development.
Improved simulation to help design microfluidics. Currently, simulation can model small micro-fluidic components, such as individual bends and corners, but not whole fluidic pathways, especially in complex situations that include 2 phase flow with diffusion and heat transfer models. Experience is required to get the first models close to the desired performance. Such a model will be computationally demanding, requiring 1-3 days to return solutions, and therefore unsuitable for design optimisation. The development of quantum computing will offer much higher computational power, significantly reducing the required simulation time. This area is more of a longer-term development space.
New manufacturing methods. The materials used will change and get better, with benefits such as no shrinkage, reduced residual stresses, and full transparency without autofluorescence. Microinjection melding tolerances will decrease and offer part finishes of higher flatness. More reproducible chips will be produced that allow good bonding of surfaces with much higher yields than currently possible. 3D printing will be used for high resolution 3D features, which will allow rapid prototyping of complex topologies and with additive extra elements, accelerating product development. Moreover, this technology will offer better interfacing solutions for microfluidics with the macroscopic world (e.g. manifolds/cartridges) since it will remove the need for interfacing geometries and alignment topologies that increase the dead volumes. This results in some cases in larger than total desired volume for processing. New manufacturing methodologies are more of a medium-term development.
Passive valveless fluidics. Use of precisely deposited chemical treatments will change the surface properties of the microchannels to drive liquids leveraging capillary action. Moreover, passive valves based on modified surface properties will enable the precise flow control of liquids through the device, enabling sequential liquid manipulation (reagents introduction) without requiring external power consumption.
Pumping using non-mechanical mechanisms. Examples of these mechanisms include electro-wetting or Magneto-hydrodynamic (MHD) mechanisms. These can be miniaturised more easily than

mechanical devices. The key challenge will be increasing the flow rate and pressure from the pump. This can be a medium-term development space.

AI/data handling

Digital Twins. DNA sequence (and diagnostic data) digital twins can prove to be very useful in healthcare applications. Patient data can be analysed via their digital twin and compared with millions of genetic diseases in real time. This can allow health care providers to monitor patients better and enable preventive measures to reduce the risk and impact of the disease. The challenge is a large upfront cost for data collection devices and the related infrastructure. Digital twins are a medium-term development area.
Computer Vision. AI-based image recognition, classification, or segmentation can enhance healthcare diagnostic tools. Such technology can provide fast, accurate, and inexpensive solutions to diagnostic needs. For example, cancer cell detection, tumour type detection, and therapy recommendation all can be done with a sophisticated AI-powered system. The challenge is that to build robust models, real-world diagnostic images labelled with the corresponding disease or condition would be needed. Due to regulations around healthcare data, obtaining such data is difficult. Computer vision is a medium-term development.
Virtual Data Generation. AI-driven models can create virtual data when trained on a limited amount of real-world data. Health kit models can create 100-fold virtual data that can be used by medical device developers that utilise virtual patients for data-driven clinical trials, thereby shortening the time-to-market for medical devices, accelerating medical innovation, and significantly reducing costs. This can be developed in the short term.
Smarter Auto-Injectors. Smart injectors can be designed to deliver the prescribed drugs to a patient based on the need rather than by standard daily dosing regimens. Smart injectors can be equipped with real-time multiplex biomarker monitoring to predict the time and dosage of the drug delivery. This requires the collection of population health data and then training the algorithm model to react to individual needs. The models continuously learn to adapt to the individual's habits and life-style routines to deliver accurate dosage at the optimal time. The challenge is that creating such a solution would require a complex amalgamation of hardware, software, and AI capabilities whilst accommodating regulatory requirements. These can be medium-term developments.
Improved precision medicine. The convergence of AI and precision medicine promises to revolutionise health care. Precision medicine methods identify phenotypes of patients with less common responses to treatment. AI then leverages sophisticated computation and inference to generate insights, enabling the system to reason and learn, and hence empowers clinical decision-making. The output is more nuanced therapy than currently offered by standard clinical prescribing protocols. The challenge is the large upfront cost for data collection devices and the related infrastructure that is needed for real-time validation of prescribed medicine. Improved precision medicine will be available in the medium term.
Natural Language Processing. This is a field of AI that acts as a bridge between human language and machine language. Chatbots powered by NLP can help patients get instant medical help without having to involve care professionals. A chatbot listens to a patient's symptoms and health concerns, then guides that patient to the correct care based on their diagnosis. The challenge is language data collection and algorithm design, but should be resolved in the medium term.
AI in device based "health kits". The goal of health kits is to get the right treatment to the right patients at the right time, by using AI to produce better treatment through previously undiscovered insights identified by deep learning or computer vision. Patients can store all their health records in one secure

database and without any manual intervention. AI can identify health alerts and request check-ups and schedule appropriate appointments with specific care providers for the patient. The use of secure databases will help to resolve data privacy issues. The challenges are that biomarkers suitable for simple device-based assessment are limited, and a complex infrastructure needs to be established – these are likely to be resolved in the long term.
Blockchain. Data privacy is a huge issue when AI is involved. Building applications over a blockchain network may be a solution to resolve those issues. Blockchain uses a peer-to-peer decentralised networks and is nearly impossible to hack. Hence digital medical wallets are a concept that is gaining momentum. The challenge is complex infrastructure, data collection, and algorithm design. Blockchain in IVD applications is likely to be a long-term development.
Cloud vendors. Cloud vendors are aiding the demand for AI by offering tools and services that make it easier to develop, test, enhance, and operate AI systems without big upfront investments. These include hardware optimised for machine learning, AIs that automate speech recognition and text analysis, productivity-boosting automated machine learning modelling systems, and AI development workflow platforms. Cloud vendors can be incorporated into IVD products in the short term.
Next gen smart phones. AI-enhanced hardware is a key focus for all smartphone manufacturers. For example, iPhone 12 used a 24 MP camera without AI subject detection that could only produce clear images up to 10 meters. With the AI-enhanced technology, the new models can recreate the depth, width, and clarity of an object up to 30 meters with a far cleaner resolution. These types of smartphones are already having impact in other markets.

New sensors

Mass microfabrication of sensors. Mass production of sensors will be achievable through microfabrication. Complementary metal-oxide-semiconductor (CMOS) sensors (made by photolithographic methods) are now being linked to micro electromechanical system (MEMS) devices. Micromachining can create the MEMS by doing layer-over-layer deposition followed by an etching process step. CMOS plus MEMS allows new functionality (sensor and processing electronics on same silicon wafer) and produces sensors at high yields with low costs. The concept is similar to the accelerometer and optical sensors included in many smartphones and is available now in the electronics industry. Chemical sensing using field effect transistors (FETS) is also being developed, with the functionalisation being done through microfabrication.
New non-invasive breath sensors. Non-invasive sensors can detect volatile organic compounds (VOCs) that are present in breath, sweat, and urine, so could be used for passive monitoring of metabolic processes. The new gas sensors could be produced by microfabrication. They are not fully quantitative or extremely sensitive but can be used to detect trends and find significant changes. Biomarker patterns have not yet been established but AI can be used to find significant patterns. This will take ten years.
New non-invasive sweat sensors. Sweat patches that read data using chemical biosensors will lead to "clinical chemistry" on the skin. The systems could collect data over the long term and send it to cloud servers for analysis. The patches need to use flexible integrated circuits and sensors that could be very much cheaper than silicon. It will take two to five years to develop a mature process, but over five years to launch the sensors on the market. The overall concept is much less expensive than sending samples to labs for analysis.
Field effect transistors (FETs). Although these can be functionalised to specific molecules, the current issues are creating specificity in their detection, their commercial costs and how to make them last for many years. Much of the technology is being driven by electronics for smartphones. Gas sensing FETs

can be placed within mobile phones, but the current challenge is the space they require and their cost. Currently, the sensors are around £5 but will need to cost below £2 to be cost-effective. They have the potential to last the lifetime of the device that they are incorporated in.
Flexible organic electrodes. Organic electronics have the potential to be cheap and flexible components of a wide variety of different sensors. However, they currently work at low temperatures, only handle low currents, and are not yet as good as silicon. They will eventually improve and be available for the diagnostics industry. The electronics industry is the key driver, especially through developments in the mobile phone and automotive industry. IVD is a smaller market and so will have to use the electrodes that are being made available for use in other applications. These types of electrodes are a medium-term development.
Sensors for digital biomarkers. Digital sensors are currently very broad purpose and capture significant volumes of data, such as breathing and exercise – with ECG in development. Brain pattern monitoring will be available in the long term. Digital watches are continuing to evolve. Currently the model is to collect big data and transmit to the cloud where AI looks for patterns and then sends person-specific data back through the phone. Back-end processing also keeps the consumer product price down and sales high. These types of sensors are already available.
Optical sensing. Many optical sensors are available to measure heart rate, sleeping patterns, pulse oximetry, and other reflected light-based sensing parameters, such as those used in smart watches. Expansion of miniaturised optical sensors will deliver much value in the future. They are non-invasive and can live inside devices such as watches and phones without requiring external holes so maintain device integrity. They can currently use visible, near Infra-Red and longer wavelengths for interrogation. This will take two to five years to develop, potentially longer for application within IVD products.
Low-cost mass spectrometers. Mass spec sensors have already been constructed using MEMs chips. Many of the components of mass spectrometers, including mass analysers, ion detectors, vacuum pumps and gauges, and monolithic integrated mass spectrometer chips have been successfully microfabricated.
Higher levels of chip manufacture. There will be a significant increase in overall manufacture of sensing chips. Semiconductor chip manufacturing is expanding massively, is driven by communication and computing devices, plus the new entrant – the automotive industry. The ecosystem will expand, and the technology will be available for other industries in medium to long-term timescales.

Appendix E: Glossary of terminology within the Vision Statement

Vision statement

"The UK will be the industry nucleus for world-leading businesses, with the resources, skills and proven pathways for advancing pioneering technologies into successful data-enabled IVD solutions"

Industry nucleus

The cell nucleus contains its DNA. It is a cell's control centre, managing its growth and division. The UK wants to be the centre of activity for a vibrant global IVD industry as it grows and develops.

World-leading businesses

The UK wants to create global businesses which define the future of the IVD industry worldwide. It also wants to attract businesses from around the world to the UK.

Resources

The UK wants to provide the support, including the finance, equipment, and supply chains, needed to build and grow existing and new IVD businesses.

Skills

The IVD industry needs expert, experienced people to thrive. The skills needed span disciplines from pathology to genomics and data science to regulation. The UK must train and retain people with these skills.

Proven pathways

The UK needs a strong ecosystem to support growing IVD companies, with collaborators and partners such as laboratories, hospitals, universities, regulatory experts, and investors. The route from technology to products and services that are used clinically needs to be robust and easy to navigate.

Advancing

Technologies can demonstrate promise but need significant development to reach the performance required for clinical and commercial application. The UK must be somewhere early-stage technologies can be developed, technically and clinically, to achieve commercial success in ambitious timescales.

Pioneering

New, sizable markets are built around concepts which bring about change, for example, integrating genomics into clinical pathways that currently rely on traditional tissue-based histology. The UK wants to lead the global industry to build these new high-risk, high-reward markets.

Successful

The UK wants to target opportunities that significantly impact patient outcomes as well as being commercially successful.

Data-enabled solutions

The value of IVD products lies in the data they produce to inform patient-specific clinical actions. Products and services must generate high-value data to inform specific decisions about treatment.

Appendix F: Acknowledgements

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It is only by working together and partnering that we can make the high-risk opportunities happen which will truly move the IVD industry forward.

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