

Stratified medicine in the NHS

An assessment of the current landscape
and implementation challenges for
non-cancer applications





The ABPI represents innovative research-based biopharmaceutical companies, large, medium and small, leading an exciting new era of biosciences in the UK.

Our industry, a major contributor to the economy of the UK, brings life-saving and life-enhancing medicines to patients. Our members supply 90 percent of all medicines used by the NHS, and are researching and developing over two-thirds of the current medicines pipeline, ensuring that the UK remains at the forefront of helping patients prevent and overcome diseases.

The ABPI is recognised by government as the industry body negotiating on behalf of the branded pharmaceutical industry, for statutory consultation requirements including the pricing scheme for medicines in the UK.

The ABPI is grateful to Concentra for its contribution to this work and for developing the report.

Foreword



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Research is well underway to develop sophisticated methods for identifying patient populations who will most likely respond to specific interventions. Cancer applications have led the way for stratified medicines, with several stratified cancer medicines in use within the NHS. On the other hand, particularly for non-cancer applications, there is less clarity around which stratified medicines are currently being researched and developed and how they are being deployed in the NHS. This report aims to provide a baseline understanding of the use of stratified medicines and companion diagnostics in the NHS.

The UK is committed to being a global leader in the development of stratified medicines, which will offer significant benefits to the healthcare system and UK plc. We are uniquely placed to accelerate the application of stratified medicines because of our academic and industrial research base and the unique potential of the NHS as not only an engine for research and innovation, but also a leader in the delivery of that innovation. Ultimately, the use of stratified approaches is about ensuring that the right patient gets the right treatment at the right time. The discovery, development and use of stratified medicines requires a balanced ecosystem based around partnership with many stakeholders including scientists, clinicians, patients, regulators, the NHS and payers all working together.

Foreword



Stephen Whitehead,

Chief Executive, ABPI

Stratified medicine has real potential to change the way we think about, identify and manage problems with our health. The ABPI believes that the UK has an exceptional opportunity to realise the benefit of stratified medicine for all stakeholders, not least patients.

A stratified approach to medicine has already proven beneficial in the treatment of a number of cancers, and researchers are identifying more and more biomarkers that could be used to refine treatments in the future. What is less acknowledged is the rising number of non-cancer stratified applications in development and – just as importantly – those which are already in use in the NHS, helping to deliver the right medicine, to the right patient, right now.

This report provides an understanding of the current non-cancer stratified medicine landscape in the NHS. The knowledge gained from this will help us all to take the next steps needed to take full advantage of the opportunity presented by stratified medicine.

Progress in stratified medicine has been made possible through a strong alliance between industry, the NHS, funders of biomedical science and the regulator. It is this partnership that will continue to provide the springboard for further success, ensuring full engagement of all parties dedicated towards a single goal: improving health outcomes for patients.





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Introduction

The ABPI believes that a focus on stratified medicine development, as part of an integrated stakeholder healthcare strategy in the service of patients, continues to represent a major opportunity for the UK to demonstrate world-class leadership.

There has been a great deal of anticipation around the potential benefits of stratified medicine. While there have been some significant success stories in clinical practice, these are fewer than would be expected more than a decade after the completion of the Human Genome Project¹. There is a lack of clarity on what stratified medicines are currently being researched, developed and implemented into the NHS, and as cancer applications have been the exemplar for stratified medicine, this concern particularly applies for non-cancer applications.

This report responds to this concern by building a baseline understanding of the current landscape and provision of non-cancer stratified medicine in the NHS.

Background

Much of medicine involves the stratification of patients into sub-groups for diagnosis and treatment. However, the term ‘stratified medicine’ has evolved to mean something more specific, reflecting transformation in stratification enabled by advances in molecular biology. There are several variations in definition; the most prominent are outlined in table 1. The definitions have in common the notion of tailoring medical treatment to unique, often molecular, characteristics of patients through the use of diagnostics.

The terms stratified medicine, personalised medicine and precision medicine are often used interchangeably in the literature. This report uses the simple definition of stratified medicine as ‘the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of medicines or medical devices that are unique to a patient, but rather the ability to classify individuals into stratified subpopulations that differ in their susceptibility to (or severity of) a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit,

sparing expense and side effects for those who will not². Critically, it also involves the development, validation and use of companion diagnostics to achieve the best outcomes in the management of a patient’s disease or future prevention.

A stratified approach has proven beneficial in a number of cancers and genetic diseases, and researchers are working to identify more and more biomarkers that could be used to refine treatments in the future. The ultimate aim of a stratified approach to medicine is to enable healthcare professionals to provide the ‘right treatment, for the right person, at the right dose, at the right time.’

Leveraging the continuing scientific advances in genomics, molecular biology and medical technologies to detect and classify diseases more objectively lies at the heart of stratified medicine. While this report uses the word ‘stratification’ to describe this molecular sub-classification of disease and disease susceptibility using both biomarkers and a description of the phenotype, it is important to note that stratification more broadly is not limited to molecular technologies. Advances in all these areas are leading to an increase in the efficacy and effectiveness of treatment, including dose selection.

Table 1: Definitions of stratified medicine

President’s Council of Advisors on Science & Technology (definition chosen by this paper)	Academy of Medical Sciences	Innovate UK (formerly the Technology Strategy Board)	International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
The tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of medicines or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.	Stratified medicine is the grouping of patients based on risk of disease or response to therapy by using diagnostic tests or techniques.	Stratified medicine is an effective therapy that requires: <ul style="list-style-type: none"> • A companion diagnostic test • A clearly identified group of patients defined by in vitro diagnostics, biomarkers, defined algorithms, clinical responses, imaging, pathology • A molecular level understanding of the disease • Availability of both tests and medicines to clinicians 	Stratified/personalised medicine: use of genetic or other biomarker information to improve the safety, effectiveness, and health outcomes of patients via more efficiently targeted risk stratification, prevention, and tailored medication and treatment management approaches.

Methodology

While there are increasing efforts to develop the evidence base for stratified medicine, key issues and challenges exist around its implementation and adoption into routine practice. There are already established diagnostic tests

within clinical practice in the NHS, but there is a lack of clarity as to how often they are used and where the testing takes place. Access to medicine-diagnostic combinations is also known to vary geographically across the UK.

This report is based on work conducted throughout 2014. A variety of research

was conducted to build a baseline understanding of the current landscape and provision of non-cancer stratified medicine in the NHS:

<p>Desk research</p>	<p>Desk research was conducted to understand the stratified medicine context and place non-cancer stratified medicine in the context of biomarker-directed therapies at all stages of development. More than 30 reports were examined, including:</p> 
<p>Interview-based fact finding</p>	<p>Interview-based fact finding was conducted through broad engagement with over 30 organisations and 90 individuals throughout the UK, including detailed site visits to the Royal Liverpool and Broadgreen Hospitals NHS Trust and Imperial College Healthcare NHS Trust. The interview process sought to develop perspectives of the current non-cancer stratified medicines landscape from across the local health economy.</p>
<p>Pharmaceutical pipeline survey</p>	<p>ABPI member companies were surveyed to develop an understanding of the potential future demand for biomarker diagnostics required to access stratified therapies.</p>
<p>Professional opinion survey</p>	<p>Knowledge gained from the research and interview-based fact finding was used to develop a national web-based questionnaire to survey professional opinion on non-cancer stratified medicine and to build a baseline understanding of provision across the country.</p>

The national professional opinion survey was designed to develop findings regarding:

- Interest and awareness
- Implementation and access
- Perception and expectation of value
- Implementation challenges

The survey was launched on 23 July 2014. It was distributed to more than 500 stratified medicine stakeholders including researchers, commissioners, providers and industry, and additionally

cascaded through many organisations including the National Institute for Health Research (NIHR), the National Office for Clinical Research Infrastructure (NOCRI), Medical Research Council (MRC), Innovate UK (formerly Technology Strategy Board), Academic Health Science Networks (AHSNs), the Knowledge Transfer Network (KTN), the Medicine and Healthcare products Regulatory Agency (MHRA), Wellcome Trust, and the Royal College of Pathologists (RCPATH). The survey closed on 10 October 2014 with more than 300 completed responses.

Project participants

This study directly engaged over 90 individuals and surveyed over 500 individuals from the pharmaceutical industry, the health sector and academia, and was directed by a steering group of ABPI and RCPATH members. Their contribution has been invaluable and the study team would like to thank them for their commitment.



Past and present

A brief history

In 1902, Sir Archibald Garrod made the first connection between genetic inheritance and susceptibility to a disease – alkaptonuria³. His book, *The Incidence of Alkaptonuria: A Study in Chemical Individuality*, is the first published account of a case of recessive inheritance in humans.

In 1956, the first discovery of a genetic basis for selective toxicity was made. This was for the antimalarial medicine primaquine⁴.

In 1971, the first clinical study⁵ of an anti-oestrogen compound, tamoxifen, in advanced breast cancer took place at the Christie Hospital in Manchester. A second clinical study⁶ at the Queen Elizabeth

Hospital in Birmingham showed a more definitive response to the medicine at a higher dose, leading to its approval in the UK. Since then, tamoxifen's effectiveness and affordability have earned it a place on the World Health Organisation's list of essential medicines for the treatment of breast cancer in both developing and developed countries⁷. Oestrogen receptor status can be regarded as the first biomarker to direct a therapy, since oestrogen receptor positivity determined the use of tamoxifen.

In 1977, the discovery of cytochrome P450 enzymes and their role in the metabolism of medicines led to the realisation that variation in these enzymes can have a significant influence on effective dose determination of a medicine.

In 1984 planning started for the Human Genome Project with the goal of determining the sequence of chemical base pairs that make up human DNA, and of mapping all of the genes of the human genome from both a physical and functional standpoint. The project got underway in 1990 and was declared complete in 2003. It remains the world's largest collaborative biological project⁸.

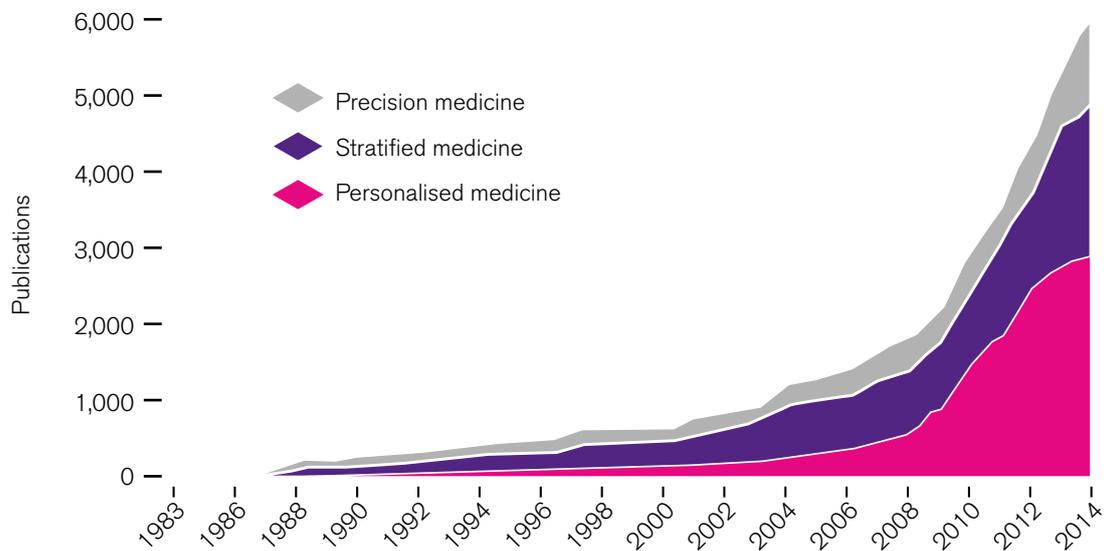
It is perhaps only in the period since the complete sequencing of the human genome in 2003 that the use of stratified medicine has begun in earnest and is now moving beyond the genome into the entire spectrum of molecular medicine, including proteome, transcriptome, metabolome and epigenome.

Recent developments



There has been a dramatic increase in the amount of research in this area.

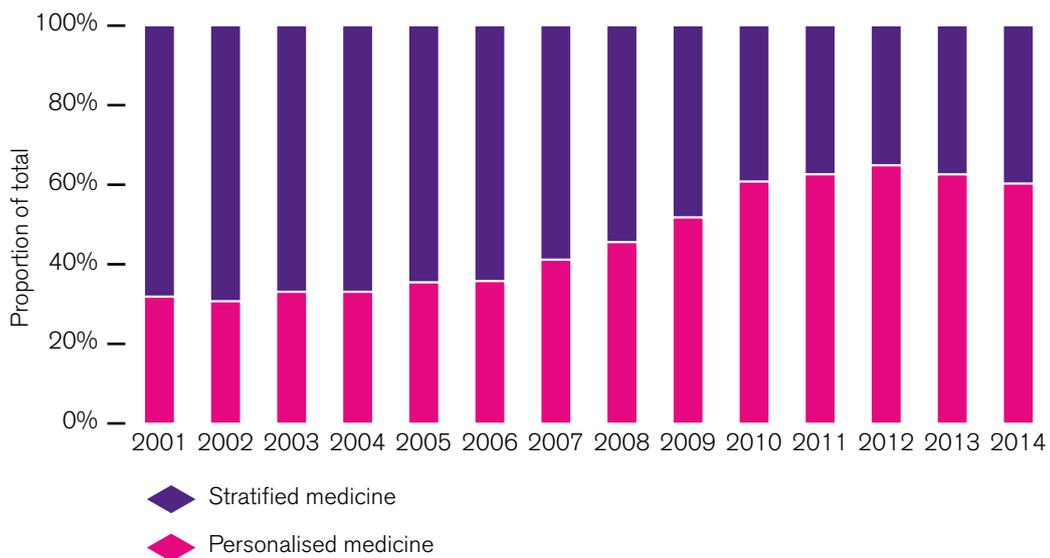
Publication keyword search results: 1983 - 2014



A publication keyword search¹⁰ was conducted to establish the number of academic articles containing the term ‘stratified medicine’, ‘personalised medicine’, or ‘precision medicine’ over the past 30 years using PubMed (a searchable database of more than 24 million citations for biomedical literature).

Note: Searches were conducted using the US spelling (‘personalized’) as well as the UK spelling (‘personalised’) to reflect the international publication landscape.

Stratified medicine vs. personalised medicine as a keyword search term: 2001 - 2014



The search term ‘stratified medicine’ returned the majority of search results in 2001. Since 2010 ‘personalised medicine’ has grown to account for the majority, indicating the trend towards increasingly accurate stratification to smaller sub-groups¹¹.

Note: Searches were conducted using the US spelling (‘personalized’) as well as the UK spelling (‘personalised’) to reflect the international publication landscape

Promise and benefits

The promise of stratified medicine

Stratified medicine has the potential to change the way we think about, identify and manage health problems. It is already having an exciting impact on both clinical research and patient care, and this impact will grow as technologies improve.

Stratified medicine promises three key benefits:

1 Better diagnosis and earlier intervention. Molecular analysis could determine precisely which sub-phenotype of a disease a person has, or whether they are susceptible to medicine toxicities, to help guide treatment choices. For preventive medicine, such analysis could improve the ability to identify which individuals are predisposed to develop a particular condition, and guide decisions about interventions that might prevent it, delay onset or reduce impact. This offers the opportunity to focus on prevention and early intervention rather than on reaction at advanced stages of disease.

“Diseases are more easily prevented than cured and the first step to their prevention is the discovery of their exciting causes.” – William Farr¹²

- Cancer example: Women with certain BRCA1 or BRCA2 gene variations have an increased lifetime chance of developing breast cancer or ovarian cancer compared with the general female population¹³. The BRCA1 and BRCA2 genetic test can guide preventive measures, such as increased frequency of mammography, prophylactic surgery and chemoprevention.

- Non-cancer example: Familial Hypercholesterolaemia is an inherited condition that causes significant elevations of plasma cholesterol and increased risk of cardiovascular disease. Mutations in three key genes have been associated with predisposition to elevated cholesterol levels. Diagnosis can lead to early intervention with cholesterol lowering treatment, which effectively lowers cholesterol concentrations and can substantially reduce the risk of cardiovascular disease. However, it is estimated that only 15% of affected individuals are clinically diagnosed in the UK.

2 Optimal treatment selection. Currently, an empirical approach is used to find the most effective medication for each patient. As we learn more about which molecular variations best predict how a patient will respond to a treatment and develop accurate and cost-effective tests, doctors will have more information to guide their decision about which medications are likely to work best. In addition, testing could help predict the best dosing schedule or combination of medicines for a particular patient. Many patients do not benefit from the first medicine they are offered as treatment. The use of genetic and other forms of molecular screening allows doctors to select an optimal therapy first time and to avoid the frustrating and costly practice of trial-and-error prescribing.

- Cancer example: Genetic testing can be used to evaluate which medicines may be the best (or worst) candidates for treating colon cancer. For example, approximately 40% of patients with metastatic colon cancer are unlikely to respond to Erbitux (cetuximab)

and Vectibix (panitumumab) because their tumors have a mutated form of the KRAS gene¹⁴.

- Non-cancer example: Abacavir is a nucleoside analogue reverse transcriptase inhibitor (NRTI) used to treat HIV and AIDS. The main undesirable effect of Abacavir is hypersensitivity, which in rare cases can be fatal. A genetic test can indicate a patient’s predisposition to hypersensitivity, therefore avoiding adverse events by pursuing alternative therapeutic options.

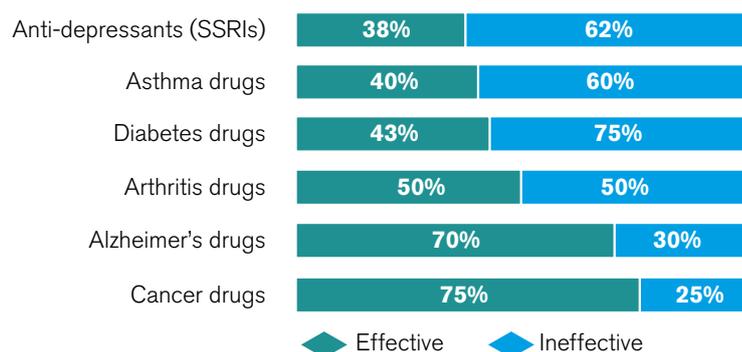
3 More efficient medicine development.

A better understanding of genetic variations could help scientists identify new disease sub-groups and their associated molecular pathways, and design medicines that target them. Molecular analysis could also help select patients for inclusion in, or exclusion from, late stage clinical trials – helping gain approval for medicines that might otherwise be abandoned because they appear to be ineffective in a larger, more heterogeneous patient population.

- Cancer example: A predictive biomarker for Iressa (Gefitinib) was discovered approximately seven years after the start of clinical trials. It then took another four and a half years of retrospective research to demonstrate significant increase in clinical benefit for those patients identified by the diagnostic test. Ultimately, the discovery of the biomarker has enabled the identification of patients most likely to benefit and offers an alternative treatment option to doublet chemotherapy in newly diagnosed advanced/metastatic non-small cell lung cancer.

Patients can respond differently to the same medicine, and many patients do not benefit from the first drug they are offered in treatment. For example, approximately half of patients do not respond to first line arthritis therapy¹⁶. The use of genetic and other forms of molecular screening allows doctors to select an optimal therapy, thus avoiding the time-consuming and costly practice of trial-and-error prescribing.

Percentage of the patient population for which a particular drug in a class is ineffective, on average



- Non-cancer example: Cystic fibrosis (CF) is a life-limiting, multisystem disease caused by loss or dysfunction of the CFTR protein. Improved understanding of CFTR protein dysfunction has allowed the development of mutation-specific, small-molecule compounds that directly target the underlying CFTR defect¹⁵. Ivacaftor is the first licensed small-molecule compound for CF patients and has the potential to be truly disease-modifying; having shown benefit in terms of an increase in lung function, decreased sweat

chloride, weight gain, improvement in patient-reported quality of life, and reduction in number of respiratory exacerbations in clinical trials. Although Ivacaftor is currently only licensed for use in approximately 5% of the CF population (those who have a specific mutation), the developmental pathway could pave the way for other CFTR modulators that may benefit more patients in future.

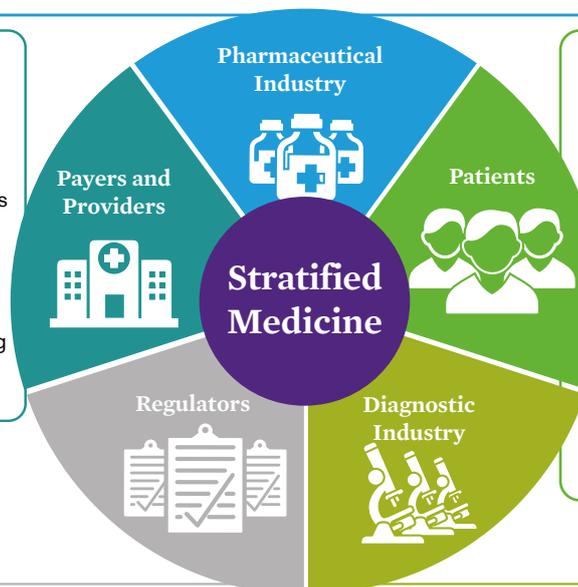
Potential benefits to stratified medicine stakeholders

The stratified medicine ecosystem covers stakeholders from across the industry, including payers, providers, pharmaceutical companies, diagnostic companies, regulators and of course patients. Stratified medicine offers different benefit potential to each, as shown in this diagram:

Stakeholder benefits of stratified medicine

- Safer, more effective medicines
- Focused discovery and development programmes based on more refined disease diagnosis
- Improved decision making and potentially lower attrition
- In the longer term, the ability to develop individual medicines with a greater value proposition with regulation and study design keeping pace (caveat: the costs of clinical trials are likely to go up in the near term with additional cost of development and validation of biomarkers required as diagnostics, and inability to pre-specify target populations accurately without a large number of patients)
- Earlier approval of new therapies with improved confidence in post-marketing pharmacovigilance systems
- More accurate targeting of the marketing of medicines
- Increased differentiation of new therapies from generic therapies leading to more valued patients thus greater likelihood to adhere to treatment

- More cost effective healthcare resources due to:
 - Improved response rates for the treatment of diseases
 - Avoidance of side effects and increased use of effective treatments
 - Avoidance of treatment for those who don't need it, or won't benefit from it
- Improved and more specific diagnosis of diseases and their prognosis leading to more accurate forecasting on healthcare resource requirements.



- Improved healthcare due to better matching of patients needs and therapeutic benefit
- Reduced likelihood of adverse events, and thus greater incentive to remain on therapy (especially for pre-morbid conditions such as hypertension and hypercholesterolaemia)
- More informed choice of therapy
- More rapid access to new and innovative medicines that work for patients
- Access to broader range of therapies supported by the NHS
- Greater personal involvement in treatment decisions and thus greater likelihood to adhere to treatment

- Greater confidence for earlier/conditional approval and thus earlier access for patients
- Greater confidence in the interpretability of pharmacovigilance data

- Increased opportunity for cost effective diagnostics to partner with the currently approved medicines and medicines in development, opening up new collaborative space with academia, patient groups, healthcare systems, pharmaceutical industry and government

Anticipating the future

Falling cost of obtaining molecular information

The pace of technological change has dramatically reduced the cost of obtaining molecular information. The Human Genome Project gave us the first complete sequence of the human genome - it cost about \$3 billion and took more than ten years to complete. Since then, the introduction of next generation sequencers has seen the cost of sequencing an entire human genome plummet from approximately £60,000 in 2000 to less than £3,000 today.

As both the cost and time involved continue to reduce, it may soon be possible to sequence genomes in hours for less than £1,000¹⁸.

The cost per MB of DNA sequence reduced from £63 in January 2008 to £2.40 in October of the same year. Today it is approaching 50p per MB.

The advent of next generation sequencing technologies has dramatically decreased the cost per MB of DNA sequence.

Between January and October 2008 the cost dropped from £63 to £2.40 – today it is approaching 50p per MB. Similarly, data storage costs have dropped dramatically: 1GB of storage cost £121,000 in 1980, this was down to £6.00 in 2000, and today it is in the region of 3p.

The cost of acquiring specific diagnostic information continues to fall as test technology improves. The current trend towards panel testing – which conducts multiple molecular investigations simultaneously – is replacing individual tests due to its ability to deliver a lower unit cost per investigation.

Increasing clinical value of molecular information

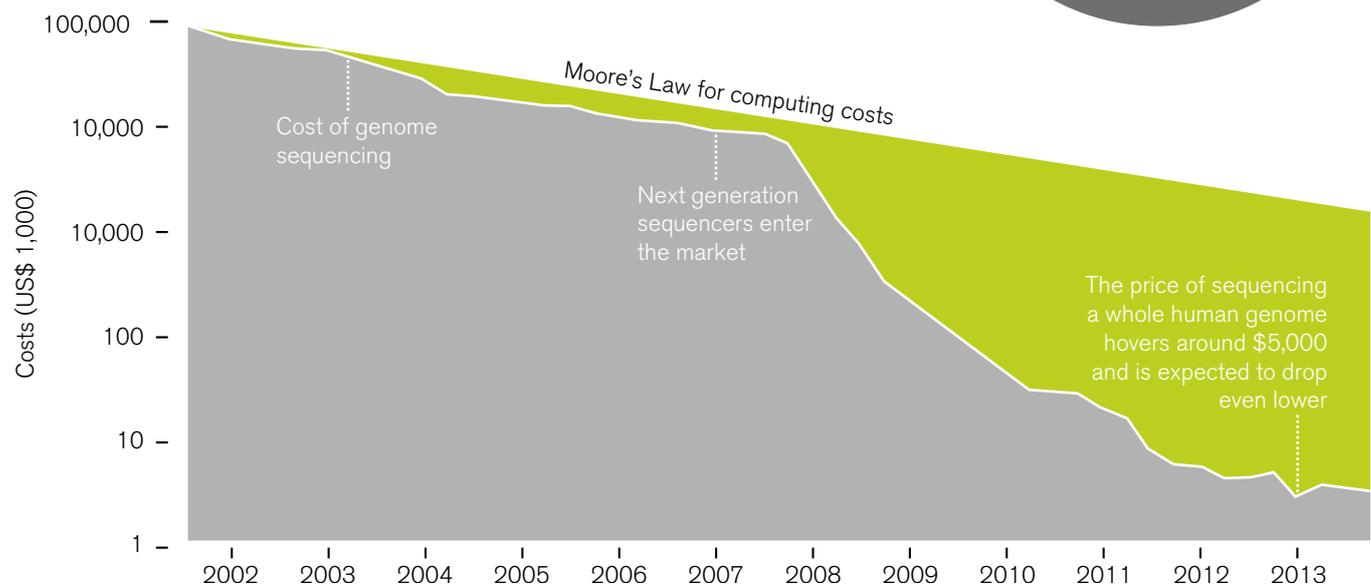
As the cost of obtaining and storing molecular information has fallen, the clinical value of molecular information has also increased substantially as an increasing number of molecular biomarkers have been found to have clinical validity.

The value of molecular information increases as new applications are clinically validated for existing biomarkers and as new biomarkers become clinically validated. In short, the more clinically valid uses we find for molecular biomarkers, the more valuable this information becomes.

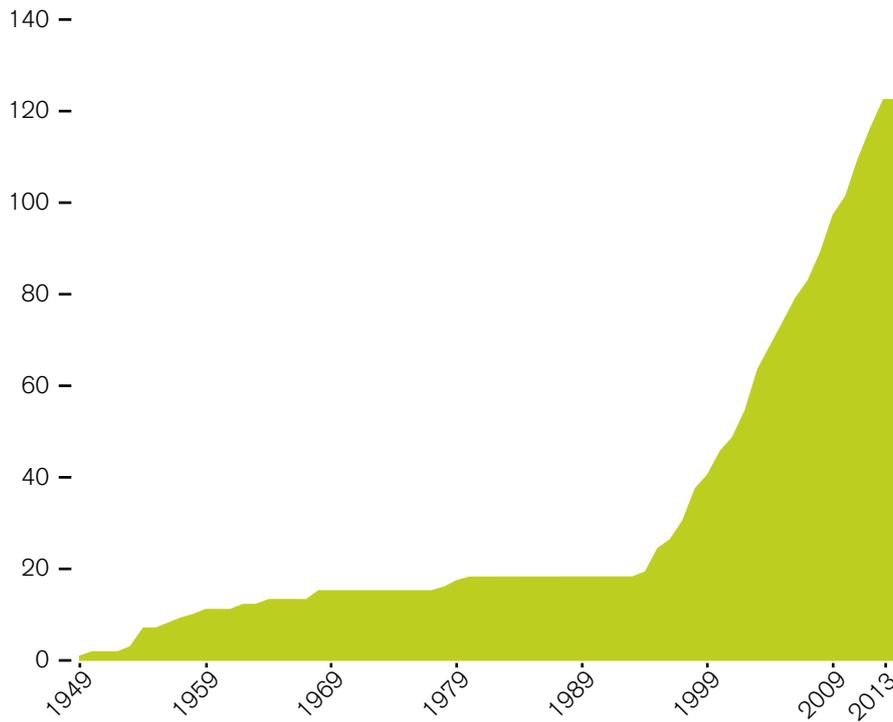
1GB
of data storage cost £121,000 in 1980, by 2000 this was down to £6.00, and today it is in the region of 3p

Falling fast

In the first few years after the end of the Human Genome Project, the cost of genome sequencing roughly followed Moore's Law, which predicts exponential declines in computing costs. After 2007, sequencing costs dropped precipitously.



FDA drug approvals requiring an associated biomarker
1949 - 2013 (cumulative total)



The number of Food and Drug Administration (FDA) medicine approvals containing an associated biomarker has increased seven-fold since 1993, an average annual growth rate of **17%**

UK genomic data = 75 days of Facebook data

How big is the big data challenge?

At the most basic level, each DNA base pair requires 2 bits of digital storage. Since there are about 2.9 billion base pairs in the human genome, (2 * 2.9 billion) bits ~ 691 Megabytes (MB). In reality, slightly more than 2 bits are required since a 'storage overhead' is created by other bases in sequence information. As a result, the amount of raw storage has been estimated at 750-770 MB.

To put this in context:

- The hard disk on a typical PC can store 500 Gigabytes (GB) of data (equivalent to 500,000 MB). This is enough to store the full genome for more than 650 people.
- To store genomic data for the entire population of the UK would require just over 46 million GB, or 46 Petabytes (PB) of storage. It may sound a lot, but this is only 15% of the size of the data warehouse that Facebook uses, which holds some 300 PB of digital information. Google processes this amount of data every two to three days.

- Facebook stores 600 Terabytes (TB) of data every day. If the UK were to accumulate genomic data at the same rate, we would have genomic data on the entire population after 75 days.

Today retrieval, not storage, is the main issue. Clinicians need to make time-sensitive decisions. Making use of this vast amount of data takes time and is not easily made available at the point of care. The challenge is how to analyse, synthesise and package the information in a way that is useful for healthcare professionals – when they need it.

Non-cancer stratified medicine baseline

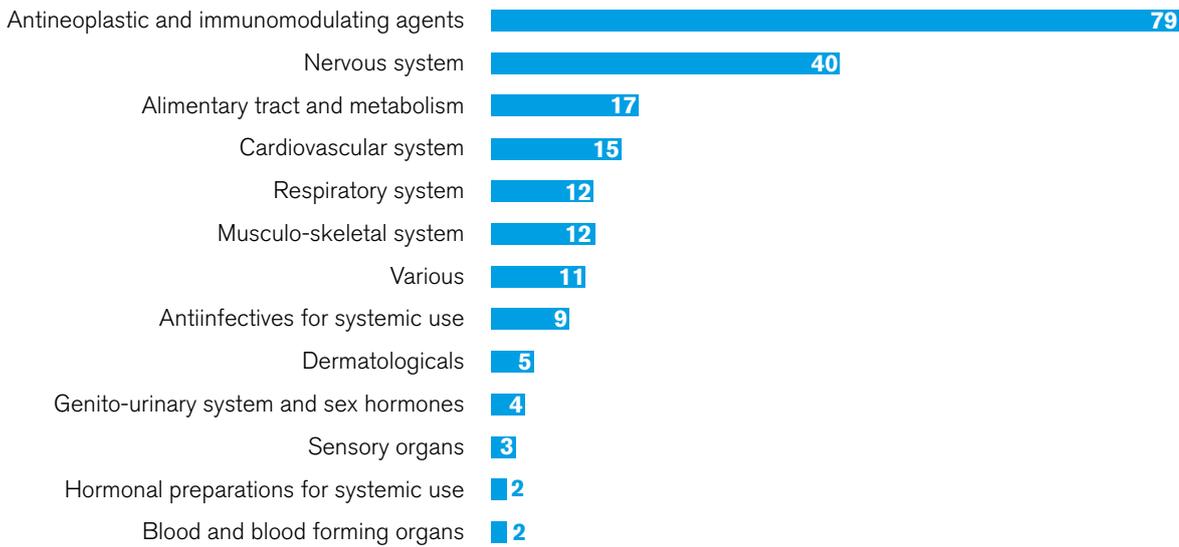
Current landscape

As previously mentioned, stratified medicine promises three key benefits: better diagnoses and earlier interventions,

optimal treatment selection, and more efficient treatment development. The pharmaceutical industry's focus on products associated with biomarkers summarises the industry's perceived value

in stratified medicine. There are currently over 200 biomarker-directed therapies at all stages of development¹⁹.

Pharmaceutical products associated to biomarkers (Phases I - IV)

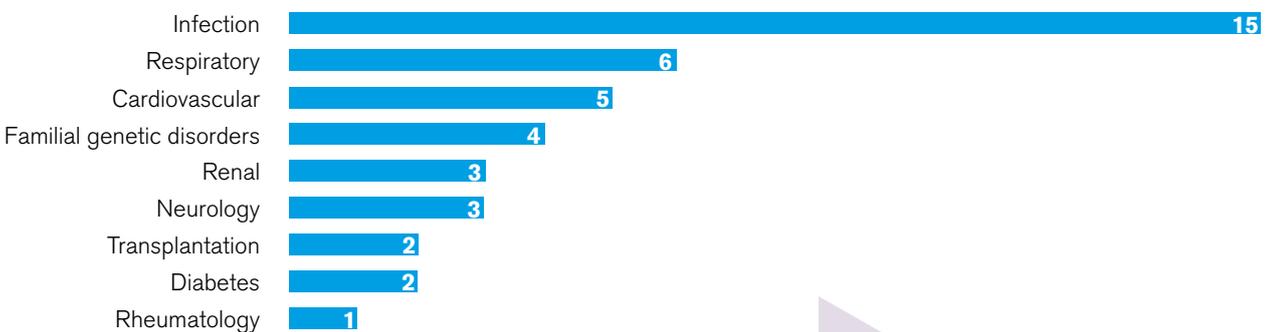


Cancer applications have led the way for stratified medicine, and near-term stratified medicine development and implementation efforts continue to focus on cancer: an assessment of 30 stratified therapies currently in pharmaceutical pipelines revealed that 27 (90%) were

cancer applications²⁰. However, less-reported and less-discussed are the growing number of non-cancer stratified medicine applications in development and being used in practice. At the outset of this report engagement within the ABPI revealed five non-cancer stratified

medicine applications at all stages of development. Engagement throughout the stratified medicine community revealed an additional 36 non-cancer stratified medicine applications for a total of 41 applications of non-cancer stratified medicine as shown in table 2.

Non-cancer stratified medicine applications provided by interviewees



Significant effort was required to discover each of these 41 applications of non-cancer stratified medicine. Interviews were conducted across a range of therapeutic areas. Some interviewees stated that stratified medicine was 'not here yet' for their given area; others listed a handful of applications in research or practice; many added the caveat that these were 'low volume' or 'very rare'. Researchers and practitioners were generally only aware of applications in their clinical area or sub-speciality; few had cross-speciality knowledge of applications, and additional research revealed no single database or consolidated perspective on non-cancer stratified medicine applications, development status, availability or use.

Few interviewees used the same definition of stratified medicine in identifying applications. Some noted that

'all medicine involves stratification of patients'; others considered a diagnostic test as a necessary component of a stratified application; some stressed a molecular-level diagnostic and therapy as a necessary requirement for labelling an application as stratified.

Equally challenging was determination of the NHS status of many of the non-cancer applications. Of the 41 applications discovered, interviewees knowledgeable about each application listed 13 as 'available' in NHS pathways, 12 as 'required' in NHS pathways, and seven as still 'in research'. Interviewees were unaware of the NHS status for the final nine applications. This unawareness of NHS status underscores a more general finding: **there was a lack of awareness and agreement amongst practitioners as to the availability of most applications within the NHS.**



Looking forward

It is expected that stratified medicine will continue to grow in applications and in use. This perspective was substantiated through a therapy-associated diagnostic demand survey sent to all ABPI member companies, which consolidated the expected future demand for stratifying diagnostics associated with 30 stratified therapies currently in development pipelines.

Results showed an expected 27% year-on-year growth in demand from new applications for stratifying diagnostics through 2018. 27 of the 30 stratified therapies were in cancer applications, further substantiating the expectation that cancer applications continue to be a key area of development focus²¹.

It should be noted that this perspective only considers new medicine-diagnostic combinations. It does not consider demand uplift from therapies currently

on the market, which are also expected to increase diagnostic test volume as equality of access expands. It is unknown whether all of these pipeline therapies will reach market and be used within the NHS. It is also unknown how many additional medicine-diagnostic therapies are in pharmaceutical pipelines and the associated incremental diagnostic test volume should these reach market, though an upward trend is expected.

Estimated incremental diagnostic test volume based on current development pipelines²¹

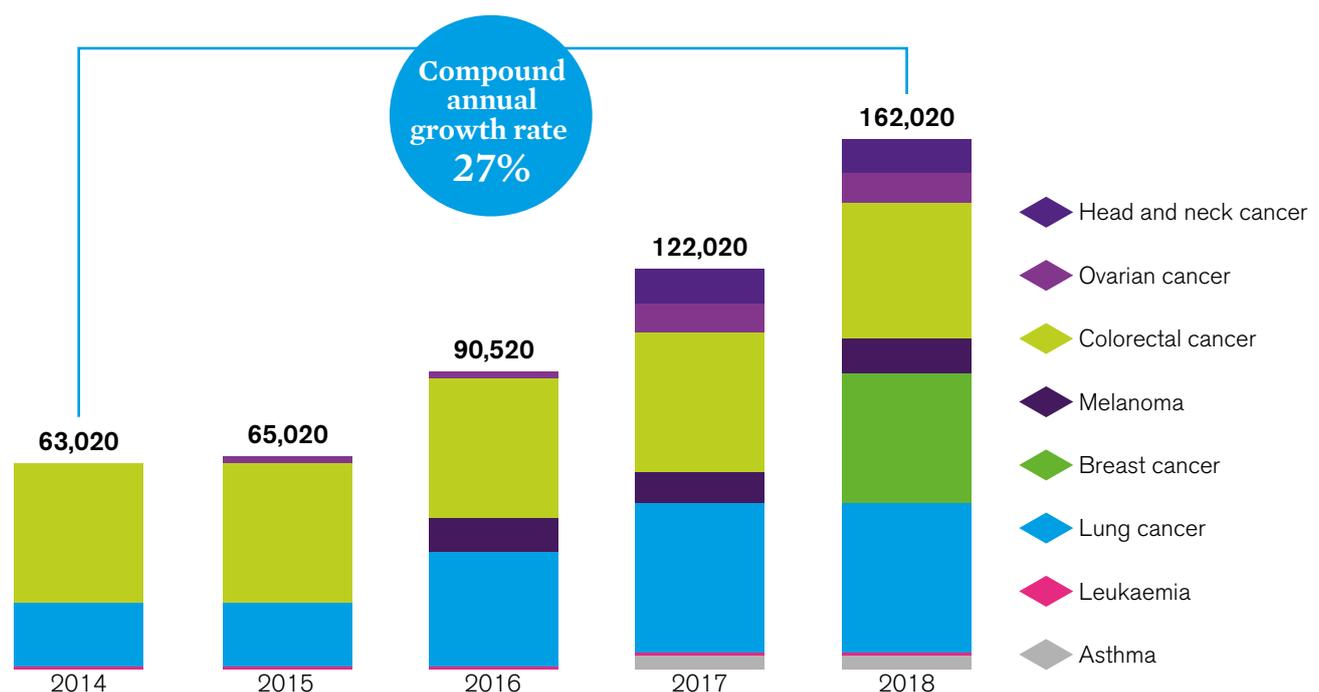
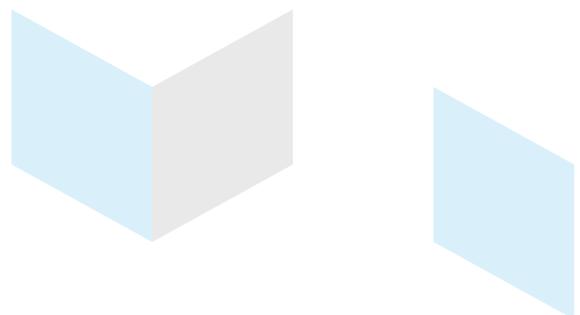


Table 2: 41 non-cancer stratified medicine applications and information provided by interviewees

No.	Application Area	Indication	Diagnostic Test	Application	Associated Therapy(s)	Reported NHS Status
1	Cardiovascular	Familial Hypercholesterolemia	LDLR, PCSK9, ApoB mutations	Screening, diagnosis	Statin	Available
2	Cardiovascular	Heart Failure	ST2 protein, BNPS	Screening	-	Available
3	Cardiovascular	Ischemic heart disease (IHD)	Coronary artery calcium score	Diagnosis	-	Required
4	Cardiovascular	Anticoagulation	CYP2C9/VKORC1	Dosing	Warfarin	In Research
5	Cardiovascular	Stroke / DVT	Cytochrome P450	Dosing	Clopidogrel	Available
6	Diabetes	Monogenetic neonatal diabetes	HNF1A	-	Sulphonylureas	Available
7	Diabetes	Maturity onset diabetes of the young	HNF1A	-	Sulphonylureas	Available
8	Familial Genetic Disorders	Factor V Leiden thrombophilia	Factor 5 leiden mutation testing	Screening	-	Required
9	Familial Genetic Disorders	Cystic Fibrosis	G551D mutation in CFTR gene	-	Ivacaftor	Required
10	Familial Genetic Disorders	Cystic Fibrosis	G551D mutation in CFTR gene	-	Lumacaftor	In Research
11	Familial Genetic Disorders	Cystic Fibrosis	m1555a	Screening	-	Required
12	Infection	Measles	Measles PCR Test	Diagnosis	-	Unknown
13	Infection	Meningococcal disease	Meningococcus PCR Test	Diagnosis	-	Unknown
14	Infection	Pneumococcal diseases	Pneumococcus PCR Test	Diagnosis	-	Unknown
15	Infection	Chlamydia	Chlamydia PCR Test	Screening	-	Unknown
16	Infection	Hepatitis C	Hep C PCR Test	Diagnosis	-	Required
17	Infection	Tuberculosis	TB Sequencing	Diagnosis	-	In Research
18	Infection	HIV	HLA-B*57:01	Screening	Abacavir	Required
19	Infection	Fungal infections	CYP2C19	Dosing	Voriconazole	Available
20	Infection	HIV	Tropism assay	Selection	Maraviroc	Available
21	Infection	HPV	HPV screening	Screening	-	Available
22	Infection	Diarrhoea (e.g. congenital chloride diarrhoea)	Diarrhoeal panels	Diagnosis, Therapy selection	-	Unknown
23	Infection	Multiple indications	G6PD	Screening	Aprimoquin (antimalarial) Rasbiracase (antigout)	Required
24	Infection	HIV	CD4	Screening	Nevirapine	Available
25	Infection	HIV	Creatine clearance	Screening	Tenofavir	Available
26	Infection	HIV	516GT	-	Efavirenz	Required
27	Neurology	Epilepsy	HLA-B*1502	Neurology	Carbamazepine	Required



No.	Application Area	Indication	Diagnostic Test	Application	Associated Therapy(s)	Reported NHS Status
28	Neurology	Epilepsy, Alzheimer's, Parkinson's and other neurological disorders	PET scan	Diagnosis, Therapy selection	-	Available
29	Neurology	Suspected stroke	CT / MRI imaging	Diagnosis, Therapy selection	Thrombolytic therapy if no haemorrhage	Required
30	Renal	IgA nephropathy	Molecular analysis	-	-	Unknown
31	Renal	atypical Haemolytic Uremic Syndrome (aHUS)	Molecular analysis	-	-	Unknown
32	Renal	C3 glomerulopathy	Molecular analysis	-	-	Unknown
33	Respiratory	Asthma	IL5 assay	-	-	Unknown
34	Respiratory	Asthma	Serum periostin levels	Therapy selection	Anti-IL13 therapies, including Lebrikizumab	In Research
35	Respiratory	Asthma, White Blood Cell diseases	Eosinophil counts	Therapy selection	Mepolizumab	In Research
36	Respiratory	Asthma	Eosinophil counts	Therapy selection	Benralizumab	In Research
37	Respiratory	Primary Ciliary Dyskinesia	Molecular analysis	Diagnosis	-	In Research
38	Respiratory	Interstitial Lung Disease	Molecular analysis	Screening	-	Available
39	Rheumatology	IgG4-RD	Molecular analysis	Diagnosis	-	Required
40	Transplantation	Autoimmune, Transplant	TPMT	Screening	Azathioprine	Required
41	Transplantation	Seropositivity (RF and anti-CCP)	-	-	Ritumimab	Available

Survey findings

As previously mentioned, knowledge acquired through desk research and interview-based fact finding was used to develop a web-based survey of professional opinion on non-cancer stratified medicine. The survey was designed to develop findings regarding:

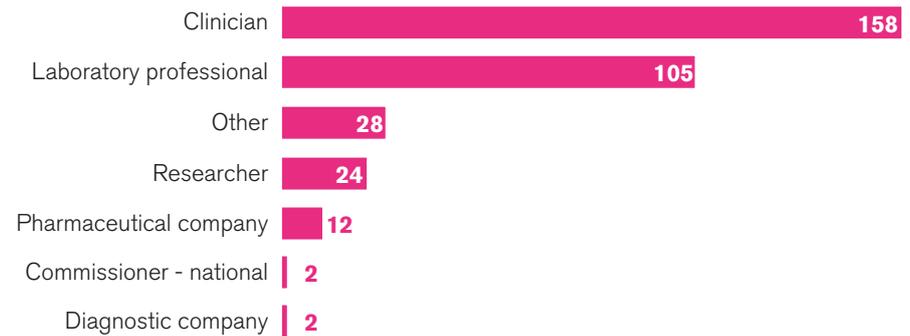
- Interest and awareness
- Implementation and access
- Perception and expectation of value
- Implementation challenges

Participants

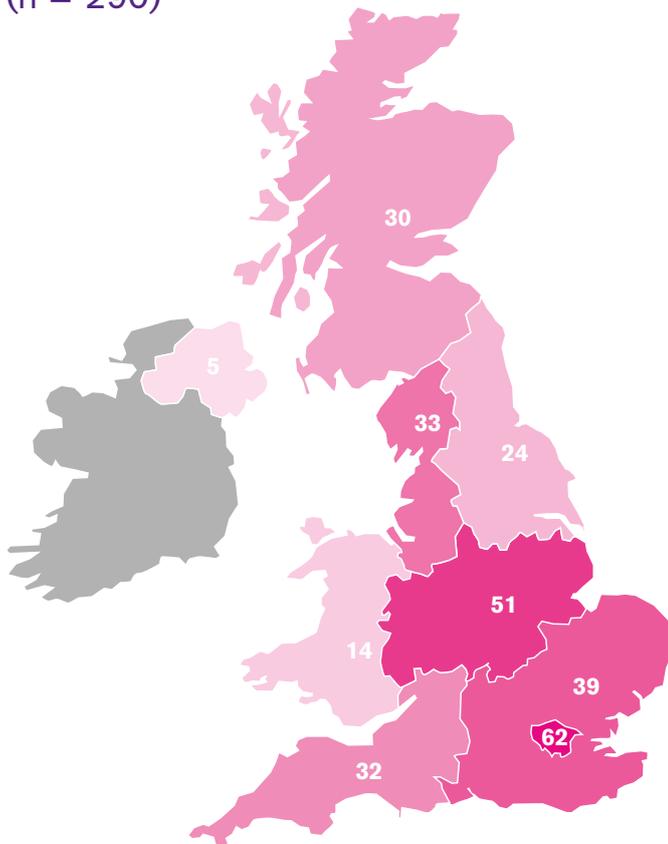
Data from over 300 survey respondents was analysed. Respondents covered a range of professional backgrounds, and were geographically located across a representative sample of regions.

Respondents reported professional interest across a wide range of application areas including infection, respiratory, cardiovascular, familial genetics, renal, neurology, diabetes, transplantation and rheumatology.

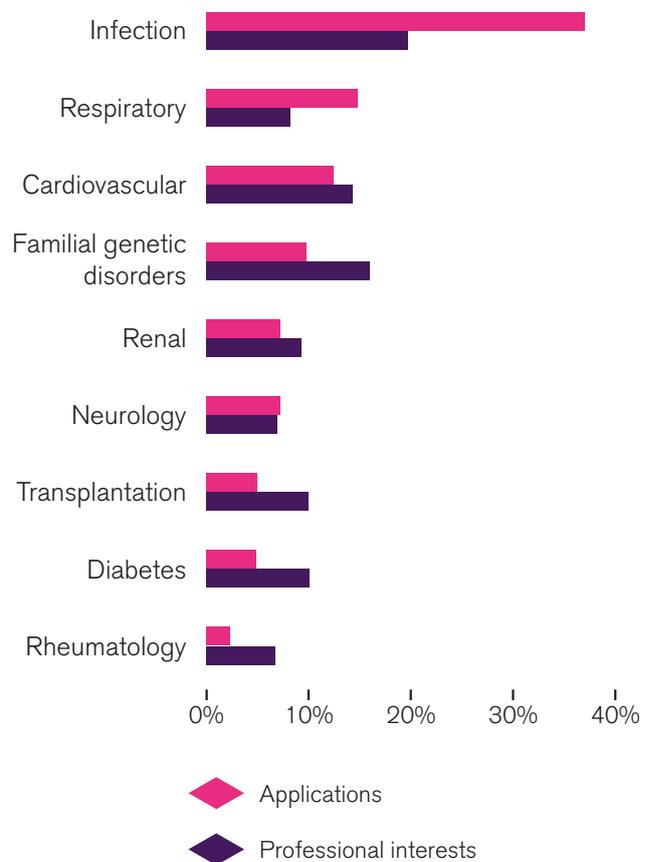
Respondents' professional background (n = 331)



Respondents' geographic location (n = 290)



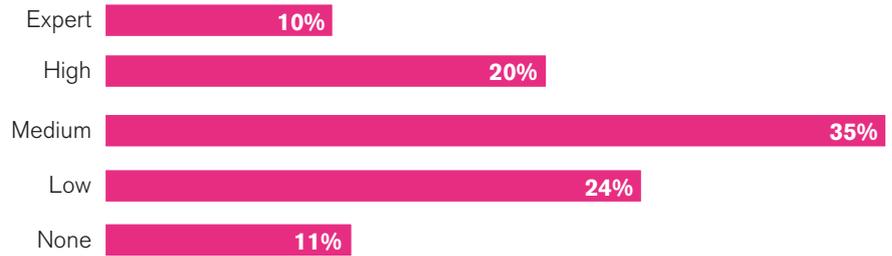
Respondents' professional interests vs. non-cancer stratified medicine applications



Interest and awareness

Respondents were generally interested in non-cancer stratified medicine: 61% reported 'high' interest in emerging uses, applications and impacts of non-cancer stratified medicine, with additional 33% reporting 'moderate' interest. Though highly interested, they were most likely to report a 'medium' personal level of awareness of the uses and applications of stratified medicine in their professional area(s) within the NHS. These findings were consistent across surveyed regions and professions.

Awareness of uses and applications of stratified medicine in the NHS (n = 233)



“In a senior position in particular it’s key to keep as up to date as possible.”

“Not all clinicians are aware of the opportunities.”

- Survey Respondents

61%

of respondents report a high interest in emerging uses of non-cancer stratified medicines



Implementation and access

Only 8% of respondents thought that stratified medicines could be considered 'widely implemented' in the NHS.

There was little regional variation in the distribution of responses to this question, although respondents from Wales and the Midlands were slightly more likely to find that stratified medicines had not been implemented in the NHS. **Overall these findings suggest that non-cancer stratified medicine implementation can be improved system wide.**

Correspondingly, about 25% of respondents said that there was 'good access' to stratified medicines, while 30% indicated that there was 'poor access'. Following the findings regarding NHS implementation, the regional differences among the responses were limited, though Scotland and the North East of England reported slightly higher access levels.

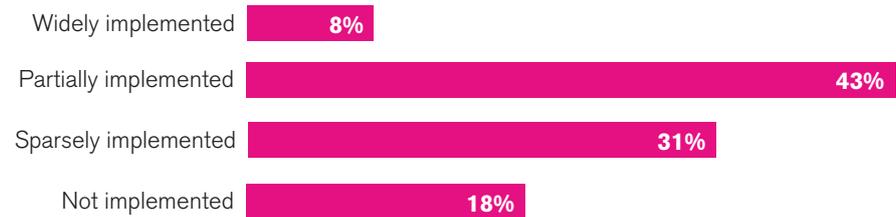
"Across the UK it is very variable with no clear guidance on the best testing strategy."

"Routes to funding lab tests is a constant issue."

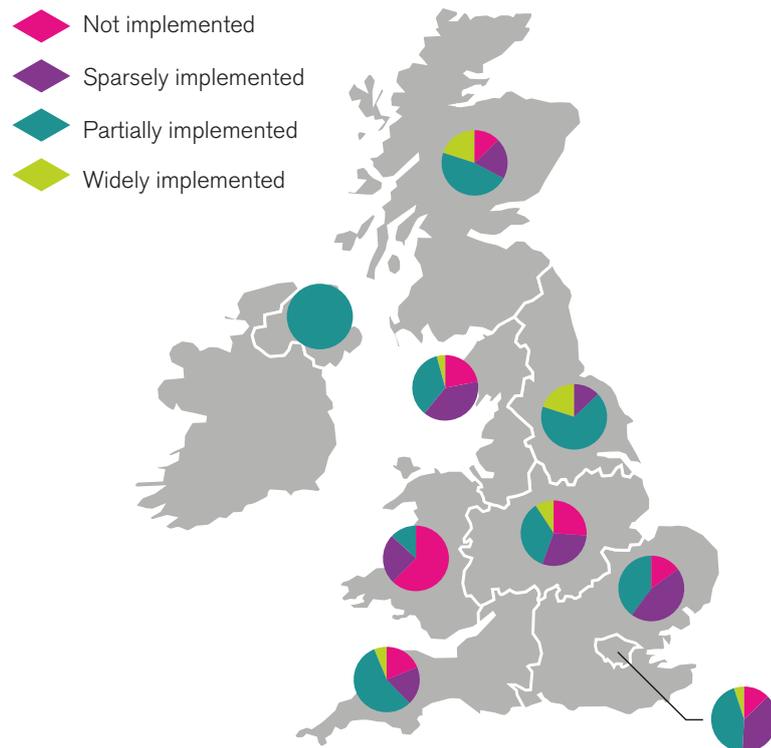
"The big issue is the clinically actionable result and the diagnostic support for it."

- Survey Respondents

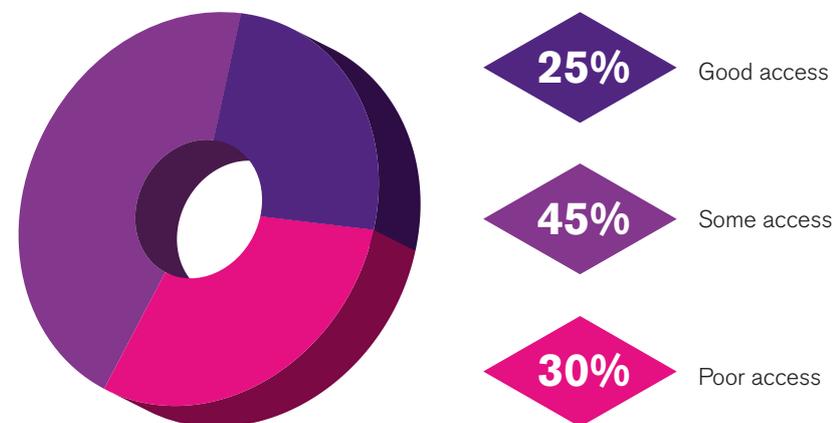
To what extent are stratified medicines implemented in the NHS? (n = 181)



Regional distribution of implementation (n = 181)



How would you rate the level of access to non-cancer stratified medicines in your area? (n = 173)



Perception and expectation of value

90% of respondents expect non-cancer stratified medicine to have a positive impact on the health system in the UK. Eight percent of respondents expect non-cancer stratified medicine to have a neutral impact. Two percent of respondents expect a mildly detrimental impact; these respondents were laboratory professionals who cited the overwhelming cost of stratified medicines as the reason for the mildly detrimental impact.

86% of respondents indicated that they expect the value of stratified medicine to increase in the next four years; 13% thought it would be roughly the same. The remaining 1% (two respondents) anticipated the value from non-cancer stratified medicines would actually decrease, citing the high cost of treatment as a barrier. One respondent specifically expressed doubt that the NHS would ever pay for the diagnostics required to access stratified therapies.

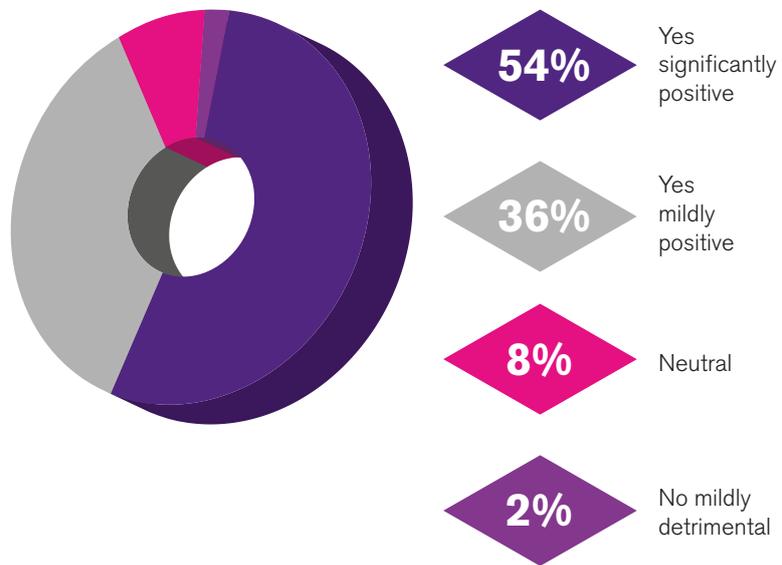
Although there is strong positive sentiment, some have been surprised that there haven't been more positive outputs from stratified medicine thus far. 97% of respondents believe the NHS is not currently maximising the potential value from non-cancer stratified medicine, with 40% of respondents claiming the NHS is 'achieving little' or 'no benefit' from non-cancer stratified medicine.

“Over the next 20 years I believe that [stratified medicine] will transform the treatment of cancer, inflammatory and autoimmune disease.”

“[Stratified medicine is] probably the most important change in the practice of medicine in the next 20 years.”

- Survey Respondents

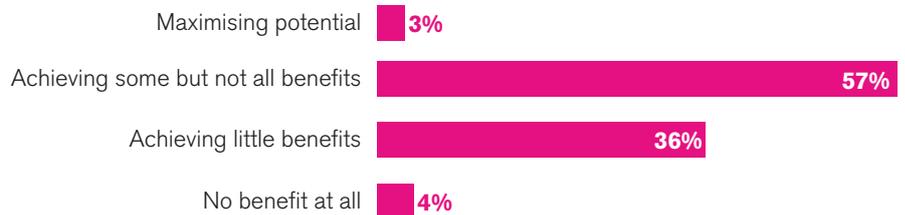
Do you expect stratified medicine to have a positive impact on the health system in the UK? (n = 167)



40%

of respondents claim the NHS is achieving little or no benefit from non-cancer stratified medicine.

To what extent do you believe that the NHS is maximising the potential value from stratified medicine? (n = 162)



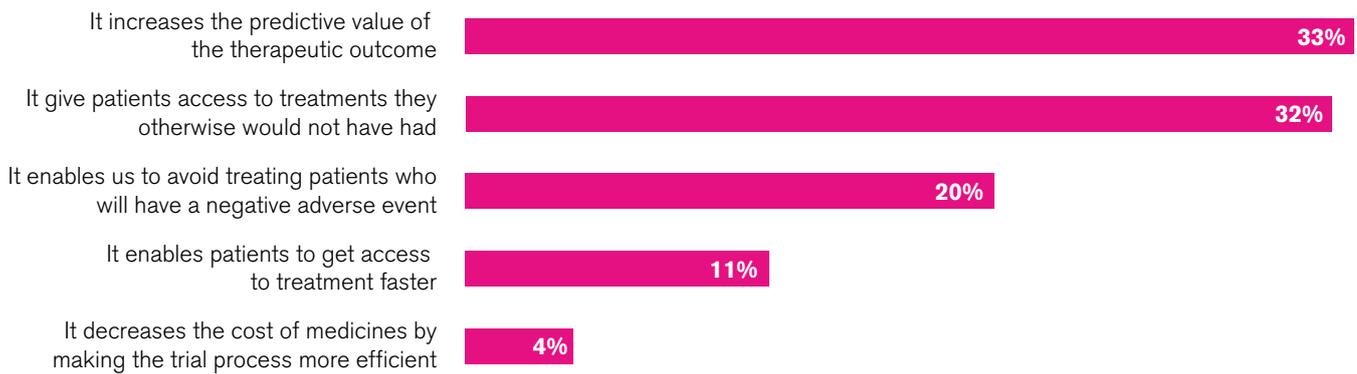
In addition to general questions on perception and expectation of value, respondents were questioned on applications in their declared therapeutic area(s) (e.g. cardiovascular, infection). Respondents were asked to list their areas of interest and provided a list of non-cancer stratified medicine application within these areas. They were also asked to select the test that would provide the most benefit to the health system.

For several of these tests respondents disagreed on test availability. Some respondents claimed that they had used these tests while others claimed they were not available. This wide variability of knowledge as to test availability was pervasive throughout the 41 stratified medicine applications listed in the survey. **On average, about half of the respondents for any given test were ‘not sure’ if it was available in the NHS.**

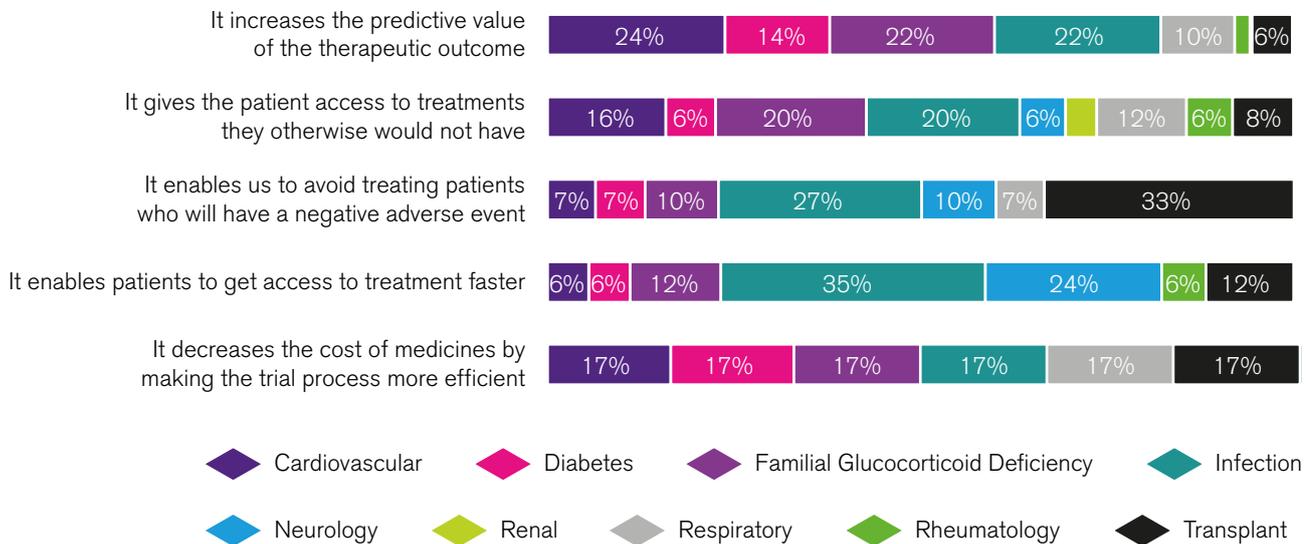
Of those that claimed to be sure, a consensus regarding availability was reached on only 13 of the 41 tests.

Respondents were also asked to list what drives the value of the most beneficial test in their area of interest. Across all disciplines, most respondents listed ‘increases the predictive value of the therapeutic outcome’ and ‘gives patients access to treatments they otherwise would not have had’ as the top choices.

Top application values across all professional areas (n = 152)



Top application values, distribution across professional areas



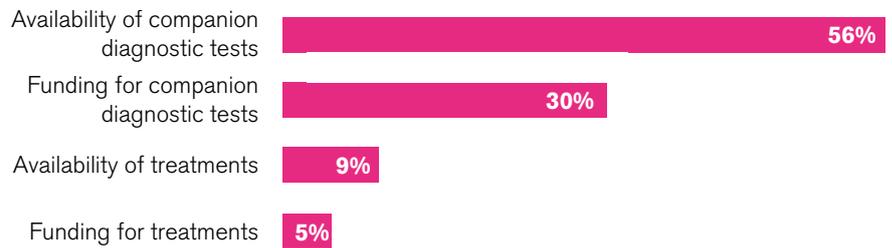
Implementation challenges

There is a high degree of alignment concerning implementation challenges. 98% of respondents agreed that there are significant challenges to implementing stratified medicine in the NHS, with 90% claiming that the health system will have to change to support the adoption of stratified medicine. There was broad agreement that treatment complexity and volumes of data will increase with implementation of non-cancer stratified medicine.

The widest barriers to access were analysed by asking respondents to select reasons stratified medicines may not be accessible in the NHS. More concern was expressed for diagnostic testing for stratified medicines rather than for actual stratified treatments. One provider focused on diagnostics as the key to unlocking value from therapies, stating that, 'We have the therapies. The challenge is that we don't know how to apply them.' These findings were consistent across surveyed regions and professions.

Both availability and funding of such diagnostic tests were listed as access restrictions more frequently than availability and funding for stratified medicine treatments combined. This was further corroborated by responses to the question 'What is needed to achieve full implementation of stratified medicine?' The top two responses were both related to diagnostic testing as part of a treatment pathway. The top item was 'reimbursement and access to diagnostics and medicines' which 133 respondents agreed was needed. The second most frequently cited item was 'medicine and diagnostic research and development,' which 90 respondents agreed was needed.

Is access restricted due to one or more of the following? (n = 137)



"Scientific evidence available, translation not always possible due either to lack of funding or clinical understanding."

"A good diagnostic network with reflex testing of all relevant molecular markers is needed and this requires a proper funding system in parallel."

"Lack of NHS IT integration and absence of bioinformatics skills."

"Communication and interaction between disciplines is required. More collaboration is required to develop a comprehensive diagnostic network."

"Simplification needed - route to testing can be too complex in particular."

"There is a need for more research on cost effective implementation and making tests available."

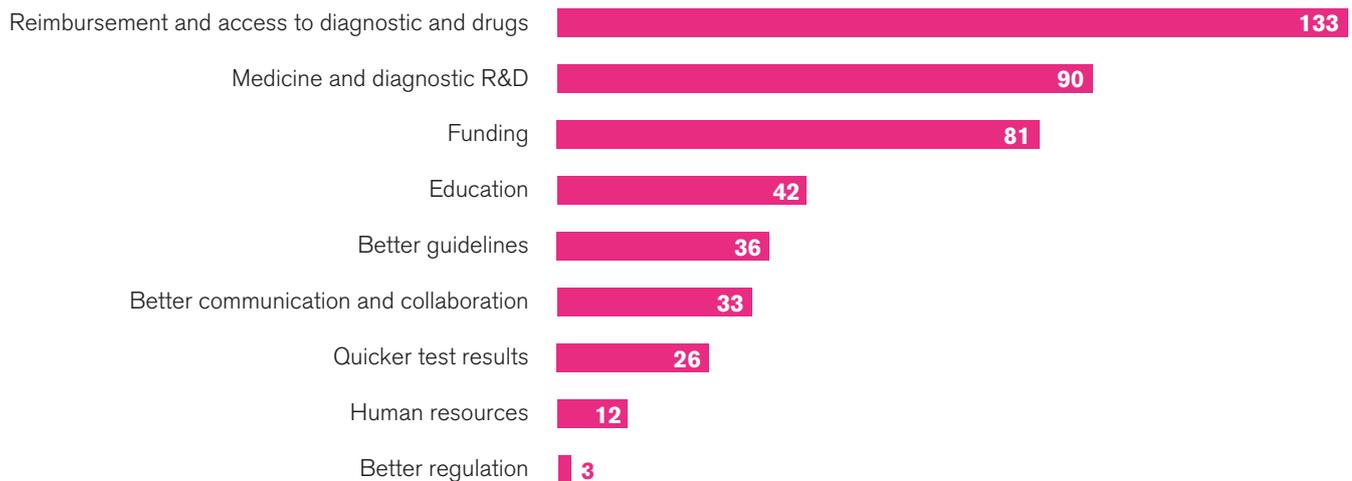
"Good information networks required to obtain outcome data. This should be through the NCIN in Oxford and data submission should be a prerequisite for reimbursement."

"There will be huge amounts of data especially as sequencing and variant analysis becomes more widespread. I am not sure the UK has the network capacity to deal with this presently. Do we need an information highway like USA?"

"Significant challenges include technology, funding, expertise, pressure from patients, etc."

Survey respondents

What is needed to achieve full implementation of stratified medicine? (n = 157)

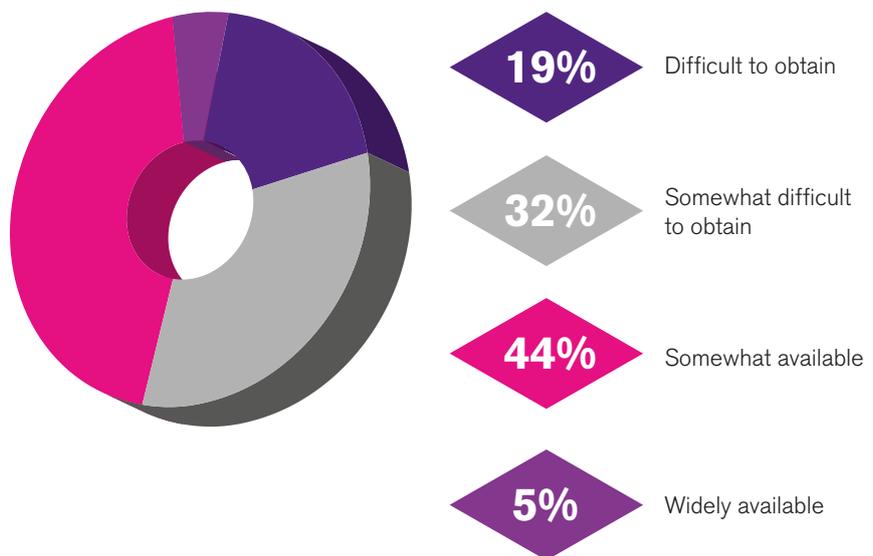


Access to information on non-cancer stratified medicines, especially from the NHS itself, was frequently cited as 'difficult' or 'somewhat difficult' to obtain. Only 5% of respondents thought that information was widely available. Sources that respondents listed as containing information regarding stratified medicines were journal articles and studies, NICE guidance, and pharmaceutical conference proceedings. Several respondents said that while information existed it was not convenient to find or use. These findings were consistent across all professional backgrounds.

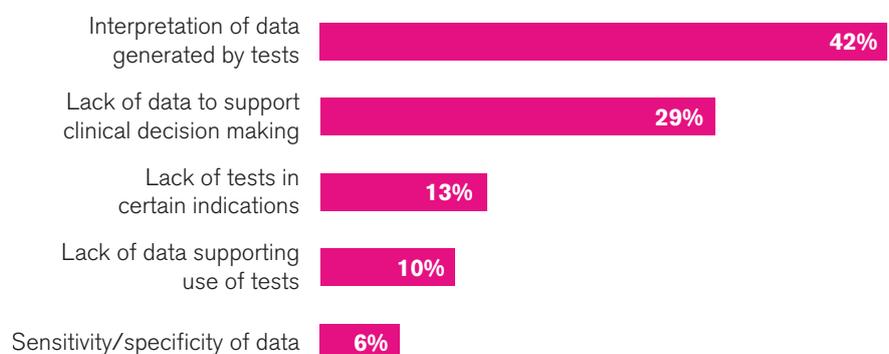
Respondents also provided their perspective on the data challenge. They pointed to data interpretation as the biggest challenge in non-cancer stratified medicine. They further listed a lack of data to support clinical decision making as another major challenge, indicating a strong interest in connecting data to practical results.

Despite these challenges, there is no doubt about the future. Stratified medicine is working its way into the NHS, it is providing value, and this value will grow.

Information about stratified medicines is...(n = 245)



What is the biggest data challenge in stratified medicine? (n=160)





Enablers

Enabling better communication and collaboration: The National Pathology Exchange²² (NPEX)

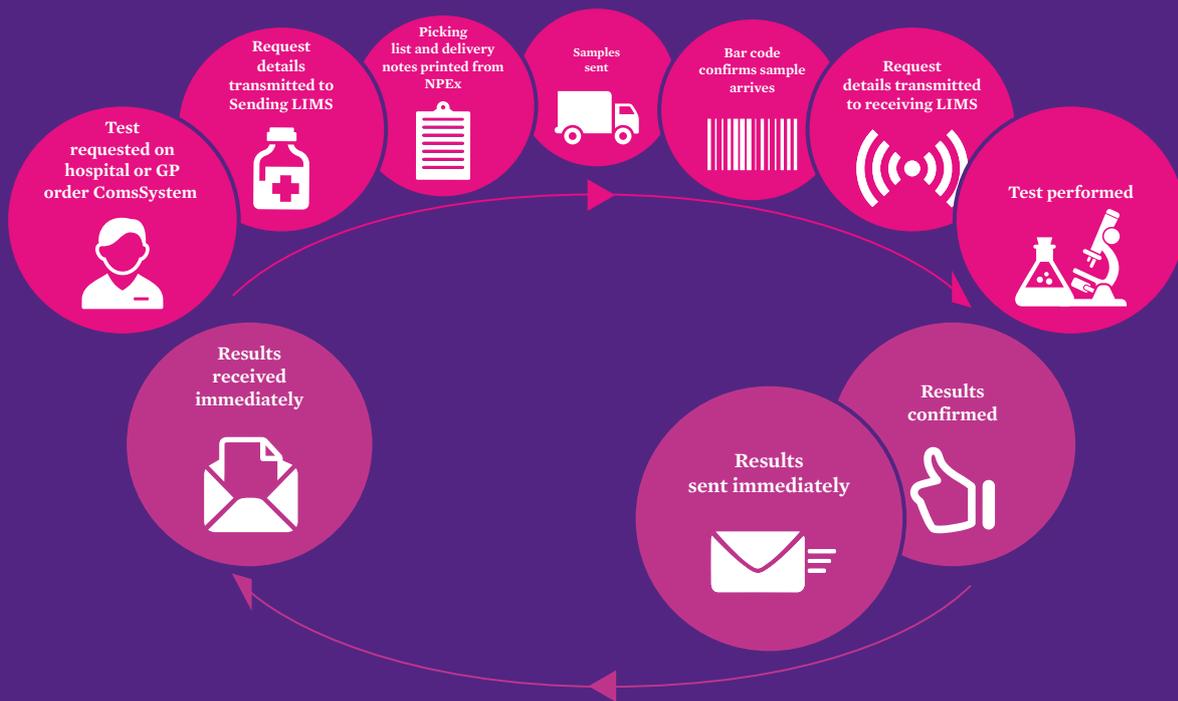
The National Pathology Exchange (NPEX) is a national service for NHS pathology managers to connect UK laboratories together through a single exchange hub so that test requests and pathology results are sent digitally from lab-to-lab. The system is designed to replace an estimated six million pieces of paper which are currently sent between NHS laboratories and being manually input into computer systems, taking an estimated 300 man years of effort and leading to a significant clinical risk from human input errors and two days delay for patients getting results²³.

With NPEX, laboratory managers can see which laboratories offer which tests for what price and can review turnaround and performance. Request details are sent electronically from the sending laboratory system to the receiving laboratory system and, once the tests are complete, the results are immediately transmitted back.

Once a laboratory is connected to NPEX it can drive out major inefficiencies by outsourcing those tests which can be done cheaper elsewhere, while retaining flexibility and capacity to respond to local demand. NPEX will help pathology departments to ensure they remain a

focal point for procurement and clinical expertise.

The cost of the NHS managing lab-to-lab referrals by paper was estimated at £2million a year in 2001. Since then lab-to-lab volumes have increased significantly, partly due to growth in demand for more testing but also as a deliberate network strategy, a recommendation from the Carter Report (2006, 2008)²⁴. The volume of lab-to-lab communications will continue to grow with the consolidation of specialist services, the rapid growth in point of care testing and the opening up of the marketplace for laboratory services.



Benefits:

- Helps deliver faster service to patients and clinicians
- Estimated cost savings £1-3 per sample – data entry, handling, postal and paper
- At least one day faster service as results received electronically and not by post
- Reduced opportunity for errors introduced during data entry
- Auditable sample trail – bar-coding used from end-to-end
- Reduces ad-hoc enquiries as electronic status checking and monitoring
- View of market intelligence supports better commissioning decisions
- Could help break down the organisational and geographical barriers to collaboration
- Roll-out of the NPEX system to date has been regional.

Enabling better data to support clinical decision making: Geneix

Geneix has developed a stratified medicine platform which has been designed for integration into digital health software tools such as Electronic Medical Record systems, digital reporting, patient platforms and clinical management programmes. It provides bioinformatics pipeline analysis of a

patient's sequenced genetic data to create their unique medicine response profile.

Each time a doctor prescribes a new medication the e-prescribing tool checks it against the patient's genetic profile. The result is an interactive and visual display of how the patient will respond. The platform also checks for medicine-

to-medicine interactions, dose safety and allergies. The benefit is a reduction in trial and error prescribing, so the right medicine is prescribed first time. The design-led approach prioritises user experience and is designed to avoid 'alert fatigue' which is a common criticism of most current e-prescribing systems.

Diagnostic Evidence Co-operatives

From September 2013, the National Institute for Health Research (NIHR) is providing £4 million funding to four Diagnostic Evidence Co-operatives (DECs) to help improve the way diseases are diagnosed. These DECs will enable experts from across the NHS and industry to collaboratively generate clinical validity, clinical utility, cost-effectiveness and care pathway benefits of in vitro diagnostics (IVDs).

All NIHR DECs will work closely with NIHR Office for Clinical Research Infrastructure (NOCRI) and link with other NIHR-funded research infrastructure.

Led by a Clinical Director and involving multidisciplinary teams, the NIHR DECs will:

- Generate high-quality evidence of clinical validity and utility, cost effectiveness and overall pathway

benefits of commercially-supplied IVDs that is sought by a range of users, including clinicians, commissioners, providers of pathology services, companies involved in CE marking and marketing of IVDs, and the NICE Diagnostic Assessment Programme

- Facilitate collaboration between stakeholders in the ecosystem
- Create new, world-class methodologies for IVD assessment, where required

Clinical Practice Research Datalink (CPRD)

CPRD provides an observational data and interventional research service through a dedicated multi-disciplinary team based at the Medicines and Healthcare products Regulatory Agency (MHRA). CPRD is jointly funded by the MHRA and the NHS NIHR.

The CPRD aims to maximise the health gain that can be achieved through the use of anonymised linked NHS data in research studies and help improve the way clinical trials of innovative

medicines can be undertaken. In so doing, it will seek to gain funding for research projects that increase the wealth of the UK as a whole.

CPRD is committed to:

- Increasing the use of the Clinical Practice Research Datalink to support public health research internationally
- Protecting the confidentiality of patient data and of healthcare professionals

- Maintaining the very highest levels of quality for data and services
- Assisting in the training of researchers who wish to use the CPRD
- Ensuring appropriate governance review and approvals for research work undertaken by CPRD and by researchers working with CPRD

Learning from past experience: National implementation of PACS

The Picture Archiving and Communication System (PACS) has revolutionised the way the NHS captures, records and uses x-rays and scans. It works with x-ray and scanning technology such as CT, MRI and ultrasound to make x-rays and scanned images available to view on screens. Clinical images are instantly and simultaneously available for study at multiple locations, supporting more effective team-working between clinicians and therefore aiding swifter, more accurate diagnosis and treatment.

The national roll-out was completed in December 2007 and the system is now in use in all acute trusts across England.

PACS has meant that clinicians are now able to access the right image in the right place at the right time.

The NPEX implementation is similarly ambitious. There is much to be learned from the PACS implementation and many reviews^{25,26} have been conducted to identify barriers and enablers to a successful roll-out. Introducing a new technology in a health-care setting is

not easy, especially on a national scale. Barriers are not only technical and financial, but also human. Enablers include strategic change management, workflow integration, benefits realisation, training and education, and system support (both technical and end-user focused).

The implementation of NPEX should make best use of the experience that the NHS has built up in successfully rolling out PACS.

Case studies

Anticoagulation

Warfarin is an anticoagulant which acts on the liver to reduce the production of key proteins responsible for blood clotting and is thus effective in preventing thrombosis and embolism²⁷. Activity needs to be monitored through blood testing to ensure an adequate dose is used; too little of the medicine could trigger more clots and too much could lead to excessive bleeding²⁸. Polymorphisms in VKORC1, which explain 30% of dose variation between patients – and CYP2C9, which explain 10% of dose variation – are particularly important determinants of dose requirements^{29,30,31}. Therefore, a stratified approach to warfarin dosing, based on genetic variation at the VKORC1 and CYP2C9 loci, in addition to clinical factors such as age and body mass index, have been suggested as a possible way of improving dosage accuracy and reducing the occurrence of unwanted effects. The effectiveness of genotype-guided dosing in comparison to standard dosing on anticoagulation control was shown recently in a randomised controlled trial³².

Reducing time and risk in treating paediatric asthma

Diagnostic-directed therapies and dosing can reduce the time required to determine the best therapy regimen and associated dosing for patients, and de-risk treatment through predicting which patients may have toxic reactions to certain therapies.

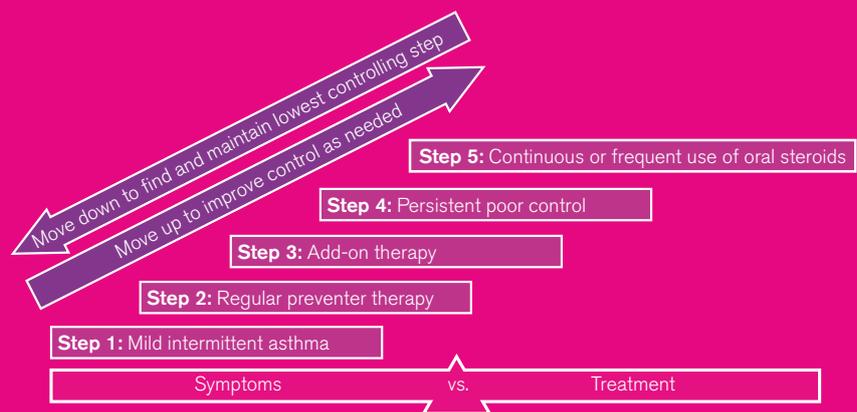
British Thoracic Society guidelines advocate a step-wise approach to asthma management for children between the ages of five to 12. This approach entails a stepped system of treatment regimens of increasing severity and risk of toxicity. It has been developed based on population evidence, but is not stratified as each patient is taken through the same approach to discover the appropriate regimen which effectively controls their symptoms and minimises toxicity. Effectiveness of a regimen is assessed every four to six months and adjusted as needed³³.

This approach is in essence a single-patient trial designed to determine the most appropriate regimen for the patient. It works; however with

assessment cycles every four to six months it can take months and sometimes years to determine the most effective regimen for a patient. In the interim, the patient suffers from uncontrolled asthma. Additionally, patients requiring more severe forms of treatment risk adverse events without clarity on whether these risks will be met with the desired outcome of controlled asthma.

However, there are limited types of asthma, with each responding differently to varying regimens^{34,35}. While the step-wise approach is a safe approach to exploring the best regimen for a patient, it could be improved through development of stratification diagnostics that would enable clinicians to identify patients likely to experience toxic reactions to certain therapies. Stratifying diagnostics could also decrease time required to determine an effective treatment regimen for the patient by identifying effective or non-effective regimens based on patient genotype and phenotype.

Summary of stepwise management of asthma in children aged 5 - 12



British Thoracic Society and Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma: A national clinical guideline. Revised 2014

Predicting hypersensitivity to HIV and AIDS therapy

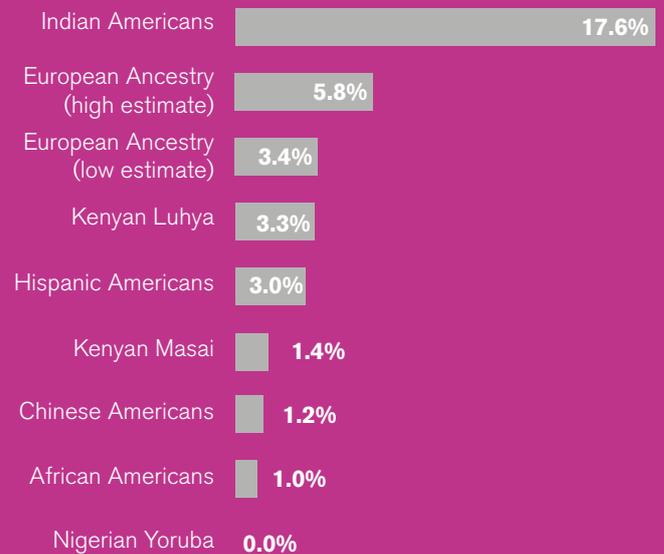
Biomarkers are often used to determine whether patients will benefit from therapies; however, they are also valuable as screening mechanisms to predict which patients may have adverse side effects if given certain therapies.

Abacavir is a nucleoside analogue reverse transcriptase inhibitor (NRTI) used to treat HIV and AIDS. It is on the World Health Organisation's List of Essential Medicines, which lists the most important medication needed in a basic health system³⁶.

The main side effect of Abacavir is hypersensitivity, with common symptoms including fever, malaise, nausea, diarrhoea, skin rash and, in rare cases, death³⁷. Hypersensitivity has been strongly associated with the HLA-B*57:01 allele^{38,39} though prevalence of the allele varies significantly across populations^{40,41,42}.

A genetic test can indicate presence of the HLA-B*57:01 allele in patients. Therefore, a stratified approach to Abacavir is required by the NHS, the FDA, and many other healthcare systems. Patients under consideration for Abacavir therapy are pre-screened for the HLA-B*57:01 allele. Those with the allele are given alternative therapy to reduce occurrence of hypersensitivity.

Hypersensitivity to Abacavir (proportion of populations)



Haematological malignancy

Thiopurine methyltransferase (TPMT) is an enzyme responsible for methylating thiopurine compounds. Thiopurine medicines, including 6-mercaptopurine, 6-thioguanine and azathioprine, are widely used in autoimmune disorders, organ transplant recipients and leukaemia treatment. Genetic polymorphisms affect the activity of TPMT and as a result, some people metabolize thiopurine medicines at a reduced rate⁴³. This impaired metabolism causes build-up of the medicine and can lead to bone marrow toxicity. In fact a small percentage of thiopurine therapies will prove dangerously toxic to the patient because of the individual's impaired ability to metabolize the medicine⁴⁴. Patients are therefore typed for their TPMT activity before being given a course of treatment. Because of the diversity of genetic polymorphisms affecting enzymatic activity, biochemical rather than genetic methods of ascertaining the phenotype are usually used.

Sensorineural hearing loss in Cystic Fibrosis patients receiving aminoglycosides

Aminoglycoside antibiotics are widely used in the management of Cystic Fibrosis (CF) to control chronic infection. However their use is associated with known side effects such as ototoxicity and renal toxicity, which must be balanced against clinical need and benefit.

Predisposition to ototoxic effects, even when levels are within therapeutic range, is associated with an inherited mitochondrial DNA mutation known as m.1555A>G^{45,46}. Screening for this mutation in individuals who will potentially receive aminoglycosides can therefore protect against ototoxicity where possible, or at least fully inform patients of the potential risk of deafness with these antibiotics. The societal costs of severe to profound hearing impairment have been estimated in a US study⁴⁷ at \$297,000 (£184,000) over the lifetime of an individual. Most of these costs are due to reduced work productivity, although special education for children contributes an additional 21%. For those with prelingual onset of deafness the lifetime costs exceed \$1 million (£620,000).

The high costs to the health service and society of meeting the needs of profoundly deaf individuals lends weight to the business case for screening costs for the m.1555A>G mutation in individuals who will potentially receive aminoglycosides⁴⁸.



Research and horizon scanning

Although the focus of this report is on the current landscape and implementation challenges, research endeavour is clearly a critical part of the ecosystem and vital to the future success of the UK in stratified medicine. The NHS is unique in its scale and structure which gives the opportunity to leverage research at population level.

The interview process identified a need for further investment and research into biomarker validation. Thousands of potential biomarkers have been identified in recent years⁴⁹, which have dramatically increased the opportunities for developing more effective therapeutics. However, the transfer of biomarkers from discovery to clinical practice is a difficult process with several limitations, mostly driven by structural and scientific factors. To become a clinically approved test, a potential biomarker should be confirmed and validated using hundreds of specimens and should be replicable, specific and sensitive. As we learn more about the science, we may learn more about the prognostic value of the original biomarker, and such new findings should be incorporated into patient segmentation of the future.

National Institute for Health Research (NIHR) Clinical Research Network (CRN)

The NIHR Clinical Research Network provides the infrastructure to allow high-quality clinical research to take place in the NHS. It helps researchers to set up clinical studies quickly and effectively; supports the life sciences industry to deliver their research programmes; provides health professionals with research training; and works with patients to ensure their needs are at the centre of all research activity.

The CRN comprises 15 Local Clinical Research Networks that cover the length and breadth of England. Each local Clinical Research Network delivers research across 30 clinical specialties.

The CRN is having a significant impact. Over 600,000 NHS patients took part in studies in 2013-14, with those recruited to commercial studies up 26% to nearly 25,000⁵⁰. Most trusts (86%) are now engaged in commercial contract research and the time taken to set up commercial contract studies was halved in 2013-14 to an average of 26 days.

NIHR Rare Diseases Translational Research Collaboration (TRC)

More than 5,000 rare diseases, or diseases that affect fewer than five in 10,000 of the population, have been identified. Although individually these diseases are rare, together they affect 7% of the UK population, they have a high impact on people's lives and collectively form a large part of the work of the NHS. The aims of the NIHR Rare Diseases TRC are to:

- Increase the volume of 'deep' phenotyping data and combine this with data on genetic abnormalities to provide greater understanding of the mechanisms underlying rare diseases and support translational research - and thereby create insights into which interventions, new or existing, are likely to be effective in preventing or treating these or other diseases.

- Facilitate tangible, rapid and efficient collaboration between NIHR-funded research infrastructure, clinical researchers, NHS organisations, other research funders and life science companies.

The NIHR Office for Clinical Research Infrastructure (NOCRI) provides streamlined and coordinated access to the Rare Diseases TRC for life science industry partners.

The Farr Institute of Health Informatics Research

The Farr Institute of Health Informatics Research comprises four centres across the UK (in London, Manchester, Swansea and Dundee). With a £17.5 million research award plus an additional £20 million capital fund from the Medical Research Council, the Farr Institute aims to deliver high-quality, cutting-edge research linking electronic health data with other forms of research and routinely collected data, as well as build capacity in health informatics research. Given the strong requirement for large-scale data analytics and bioinformatics in stratified medicine, this is a key success factor for the NHS.

The Farr Institute aims to "harness health data for patient and public benefit by setting the international standard for the safe and secure use of electronic patient records and other population-based datasets for research purposes."

An example of an initiative that is relevant to non-cancer stratified medicine: the Farr team is planning to use the Asthma e-Lab to identify genetic and environmental variables that can be measured in the first years of life (0 to three years) to predict a child's risk of asthma and clinical progression later in childhood (age five onwards). This will ultimately help clinicians to intervene at an earlier stage.

The economics of molecular testing

Molecular diagnostic test volume will increase for three reasons. First, volume for currently available tests will grow with equality of access and as new applications are found for these tests. Second, new tests will be developed and be subject to the same dynamics as currently available tests. Third, research acceleration will increase test volume for both currently available tests and new tests.

While the growth trend is strongly positive, laboratories offering a molecular diagnostic service must understand four factors, which, combined with staffing and overhead costs, determine the overall cost of their service.

Test type

Laboratories conducting molecular testing can either use commercial tests (CTs), or develop and operate their own laboratory developed tests (LDTs). The dynamics of each test type are summarised in table 3.

Laboratories unable or unwilling to use commercial tests or develop their own tests can send their samples to other laboratories. This incurs additional transportation and administrative cost vs. in-house testing, though the send-away option can still be cost effective due to sample throughput dynamics.

Table 3 Dynamics of commercial and lab-developed tests

Consideration	Commercial tests	Lab developed tests
Certification	Tests are Conformité Européenne (CE) marked	Tests are developed in-house and not CE marked
Development and validation	On average, less staff time and expertise is required at the laboratory level to validate the test	On average, more staff time and expertise required at laboratory level to develop and validate the test
Transparency	Test workings are a 'black box'	Test workings are transparent since they are developed in-house
Results	Test results are auditable across all laboratories using the test	Test results are auditable in laboratories which developed the test
Availability	Tests are available once they achieve CE mark; sometimes this can involve wait time for new tests	Tests are available once they are developed in-house
Cost	Total per-sample testing costs can be lower at low volumes and higher at high volumes. However, whole testing pathway costs can be reduced by use of better diagnostic tests (e.g. tests which achieve results faster)	Total per-sample testing costs can be higher at low volumes due to need to recuperate test development cost, and lower at high volumes due to lower reagent cost.

Sample throughput

A minimum test volume is required to perform testing in a cost-effective manner. This is dictated by sample throughput.

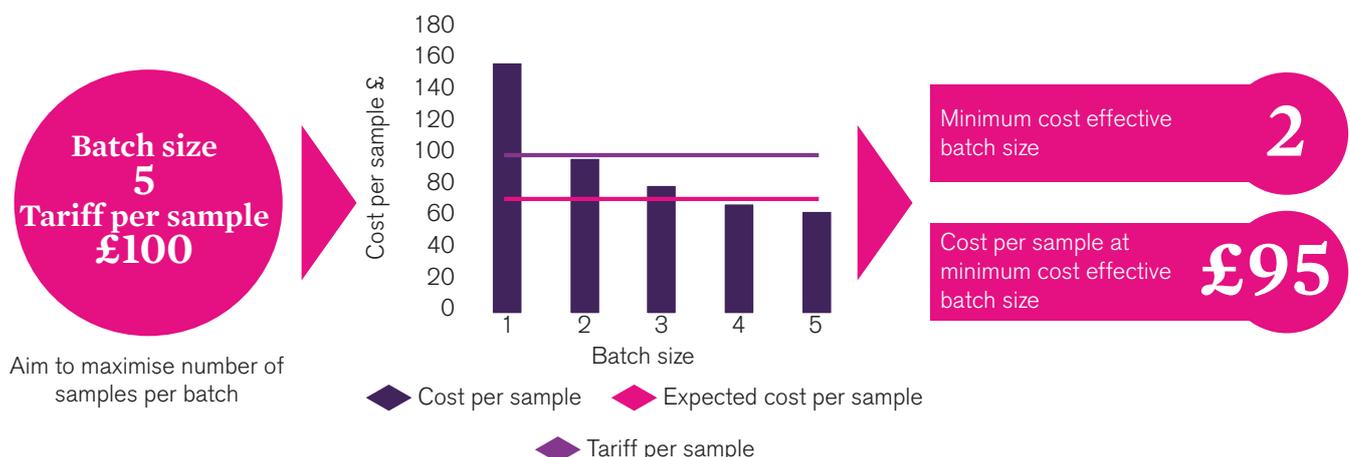
Each molecular test offered by a laboratory incurs development, validation and overhead costs which must be spread across the total number of samples tested. When the pathway involves batch

testing – for example, running a single test on multiple samples simultaneously, or running multiple samples on a multi-gene panel test – the cost of staff time for set up and operation and the positive and negative controls must be spread across the total number of samples in the batch.

The above 'fixed costs' of testing are greatly reduced on a per-sample basis if many samples are put through the

laboratory. For example, £5,000 in fixed costs create per-sample costs of £100 if the laboratory tests 50 samples, or £1 if the laboratory tests 5,000 samples. Similarly, when batch testing, the per-sample test costs can reduce dramatically if a batch is full of samples, as opposed to running with many empty wells. These economy of scale dynamics enable laboratories with higher sample throughput to offer testing at lower costs.

Illustrative example: Tariff vs cost at different batch size



Turnaround time

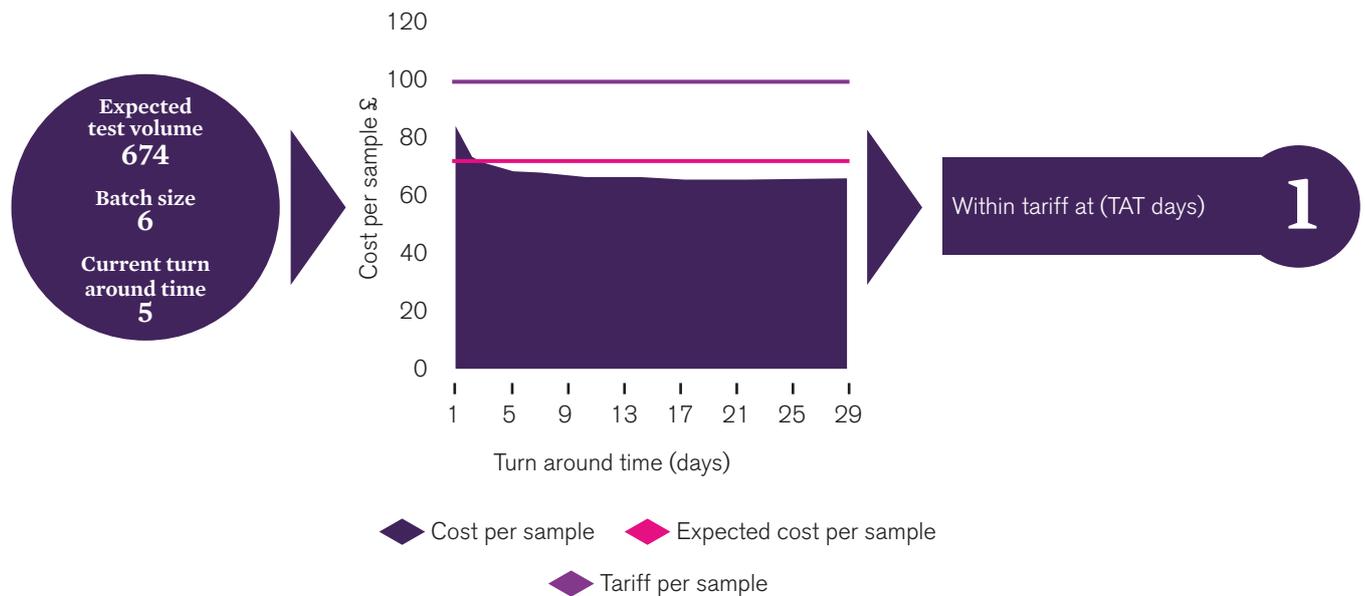
Economy of scale advantages in batch testing are also affected by turnaround time requirements. Lower turnaround times create higher per-sample testing costs as lower turnaround times increase the frequency of running partially empty

batch tests, and reduce the overall benefits of workload batching.

Laboratories with the largest sample throughput will be least affected by this dynamic, though it is important to note that some tests must be conducted in near-patient environments due to their strict

turnaround time requirements. The cost disadvantages of low turnaround times are also greatly reduced with high sample throughput, as high sample throughput decreases the frequency with which partially empty batch tests must be run.

Illustrative example: Turnaround time vs cost per sample



Testing pathway

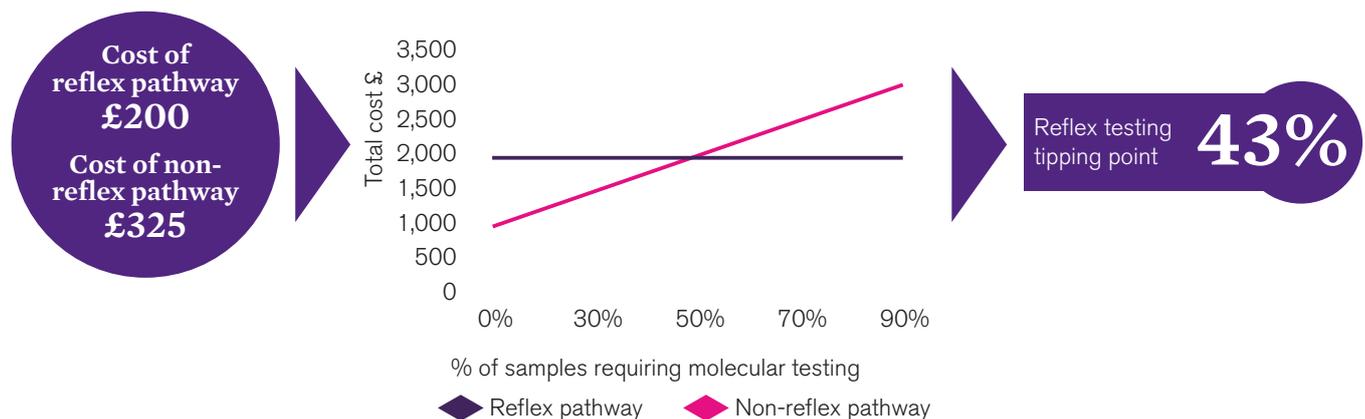
Finally, the testing pathway can itself have a significant impact on costs. Reflex testing (or assessment and prep) may reduce costs; sample handoff volume can increase costs and cause delays.

In a non-reflex molecular testing pathway, results of a cellular investigation are sent to a Multi-Disciplinary Team (MDT) meeting, which then decides if a molecular investigation is needed. If so, the sample

is then retrieved, assessed, prepped and tested, and these results are sent to the next MDT meeting. A reflex testing pathway conducts sample assessment, prep, molecular testing and results assessment by the MDT at the same time as the cellular investigation, thus reducing the cost of these activities. The trade-off is 'over testing', as MDTs do not always require a molecular investigation. However, this may be offset by avoiding additional costs incurred when cellular and molecular assessments are separated

(the key extra cost being an extra MDT). At a certain 'tipping point' a reflex testing pathway – despite 'over testing' – is overall less costly than a non-reflex testing pathway. Similar dynamics are at play if the sample is assessed and prepped for molecular testing – in case this is needed – at the same time as the cellular assessment. While this will result in 'over assessment/prep', this additional cost may be offset by avoiding additional costs incurred when samples do progress from a cellular to a molecular assessment.

Illustrative example: Reflex testing tipping point



Lessons learned from cancer stratified medicine

Three key challenges have adversely affected the implementation of cancer stratified medicine: horizon scanning, adoption of new molecular testing and clinical uptake.

While excellent horizon scanning initiatives exist, including UK PharmaScan and the NIHR Horizon Scanning Centre (HSC), none have an explicit remit to include diagnostics in their assessments. UK PharmaScan can hold information on companion diagnostics, though this information is not mandatory for inclusion with a stratified therapy. The HSC communicates with relevant bodies for stratifying diagnostics, though it does not have remit or resource to include these in their current programme. This has led to situations wherein the NHS system can be readied for a therapy and less well-informed and prepared for the companion diagnostics necessary to access the therapy. Formalisation of companion diagnostic information in UK PharmaScan may be possible; also possible would be an expansion of the HSC's remit to put

forth companion diagnostics in addition to therapies for NICE assessment.

Adoption of new molecular testing has proven an additional challenge, both in the form of lead time for test development and implementation in the healthcare scheme. Issues such as limited access, training and lack of reimbursement of diagnostic limit adoption. Slow or no reimbursement has led pharmaceutical companies to fund the testing to broaden access to the test initially reimbursement can be arranged. This has typically happened where one molecular marker links to one treatment option as a tactical response to a sub-optimal adoption process, and is not sustainable, especially in the non-cancer context. We are moving to a world where multiple tests could be used to inform treatment options, hence in the future we will need to move to centralised funding model as one test could service multiple therapeutic decisions for UK patients to benefit from access to new medicines without delay.

Lastly, clinical uptake has proven challenging in certain cases. Although the *NHS Atlas of Variation in Diagnostic Testing*⁶¹ does not currently assess all molecular tests, the variations in patient testing reported by the Atlas are expected in molecular testing, as cancer molecular diagnostic test volumes have been observed which are well below those suggested by population epidemiology. This situation is evidenced by survey respondents in non-cancer stratified pathways as well: only 8% of survey respondents believe non-cancer stratified medicine is 'widely implemented' in the NHS, with 30% of respondents reporting 'poor access' to non-cancer stratified medicine. Additionally, information is a precursor to uptake, yet only 5% of survey respondents believed good information on the uses, applications and impacts of stratified medicine in the NHS is 'widely available'. Most (76%) believe information is 'somewhat available' or 'somewhat difficult to obtain'. Remaining respondents (19%) believe information is difficult to obtain.

UK PharmaScan

UK PharmaScan is a secure horizon scanning database populated with information on new medicines in development from up to three years before their launch in the UK or start of phase III clinical development, whichever is the earlier. It forms a central repository of information, such as clinical trial

and regulatory information, to national horizon scanning groups and approved NHS organisations that have a role in supporting NHS planning, or providing advice and guidance to the NHS.

The resource is designed to help ensure earlier and more effective decision making and faster uptake of innovative

new medicines for the patients who need them. To continue to do this as effectively as possible, it is recommended that information about biomarkers and diagnostic tests is captured and presented in a consistent, structured format.

NIHR Horizon Scanning Centre (HSC)

The NIHR HSC supplies information to health policy and decision makers and research funders within the NHS about emerging health technologies that may have a significant impact on patients or the provision of health services in the near future. Their scope of activity

includes pharmaceuticals, diagnostic tests and procedures as well as medical devices, equipment and other therapeutic interventions.

The HSC provides some biomarker information currently and, resource permitting, could potentially be best

placed to provide the more detailed information that commissioners need to support the implementation of stratified medicines and companion diagnostics going forward.



ABPI recommendations

1. Horizon scanning

Improve horizon scanning to ensure commissioners and providers have the information they need to plan effectively

Stratified medicine is an emerging field which is characterised by rapid change and technical development, this creates a challenging environment in which to commission and plan services. There have been several cases of the system being 'blindsided' by medicine-diagnostic combinations coming to market, but without adequate planning to ensure that capacity is in place to meet demand, resulting in unequal and restricted access.

To address these issues, we recommend providing more structured information on biomarker-directed therapies in the development pipeline through:

- Defining the remit for horizon scanning bodies to specifically cover biomarkers, test platforms and an estimate of the service and budgetary impact of new tests
- Defining the scope of information required to support effective budgetary and capacity planning, e.g. through definition of a minimum data set

3. Uptake

Improve coordination amongst stakeholders during the launch phase to reduce barriers to uptake

There have been cases where lack of diagnostic capacity has limited access to and uptake of new medicines. Commissioners have needed to assess tests for which they have had little supporting information. Diagnostics providers have faced challenges providing tests for which there is no funding. Pharmaceutical companies have struggled to know the best way to provide support.

To address these issues, we recommend clarifying stakeholders' roles and responsibilities during the uptake phase through providing:

- A clear pathway for industry to provide support (e.g. via pump-priming), as well as guidelines on how to taper that support appropriately
- Clarity to providers on new testing requirements, and clarity on mechanisms and sources of funding
- Analysis for commissioners on new tests, including expected national volume and budget impact given efficient provision and quality standards

1. Horizon scanning

2. Commissioning

3. Uptake

2. Commissioning

Develop a coordinated and consistent commissioning approach to support networked diagnostic service provision

The commissioning and funding processes for medicines and diagnostics are often criticised as being disjointed from one another. In the past, laboratories have had to rely upon locally negotiated solutions and 'soft money' such as grants and industry pump-priming to cover the costs of diagnostic service provision. This creates incongruities wherein one part of the medicine-diagnostic combination is not funded properly.

To address these issues, we recommend a strategic framework for funding and commissioning that incorporates the following:

- Aligning the commissioning structure for therapies and their associated companion diagnostics, e.g. if a therapy is commissioned through specialised commissioning, so should be its diagnostic
- Encourage joint working between commissioners, providers and industry, e.g. to develop and assess whole pathway cost effectiveness (e.g. some diagnostics can be more expensive but reduce total pathway costs since they provide faster results)
- Create a responsive commissioning and regulatory framework that enables new technologies to supplant old technologies based on new evidence

5. Provision (pathway)

Improve management of the sample pathway to avoid delays and risks to cost and service quality

Diagnostic sample pathways often have many handovers and multiple 'owners' at each stage, which causes risk of delays and errors. For example, a survey in oncology found that 41% of delays in patient pathways are due to diagnostic sample pathway logistics. A similar pattern could emerge in non-oncology applications if left unmanaged.

To address these issues, we recommend:

- Basing commissioned pathways on standard operating procedures (SOPs) consistent with national and international guidelines, similar to the Guidance for Laboratories Performing Molecular Pathology for Cancer Patients
- Aligning and enforcing appropriate care pathways and standardised SOPs concordant with appropriate standards of care⁵²

4. Provision (network)

4. Provision (network)

Enable a networked approach to diagnostic service provision to encourage high quality, cost effective delivery

Balancing turnaround time targets and operational efficiency with disease specific epidemiology means that it will make sense for some services to be provided locally, and others to be regionally centralised.

To ensure that the quality of diagnostic service provision remains high even when elements of that service may be provided by multiple laboratories, we recommend providing direction on networked provision through:

- Commissioning pathways covering a therapy and its associated diagnostic provision
- Networking labs electronically to reduce delays and data errors (e.g. via the NPEx system)

5. Provision (pathway)

6. Decision

Improve clinical decision making by encouraging development and use of decision support systems

The number of stratified pathways is increasing, and with these the volume of information required to make clinical decisions. This information exists in a rapidly developing and changing environment, and can cascade slowly through the NHS.

To counteract issues which can arise from incomplete information and a rapidly changing environment, we recommend:

- Design and use of intelligent decision support systems (DSS) which are easy-to-use and avoid user fatigue (e.g. avoid over-abundance of alert messages)
- Promoting equality of access to approved care pathways through decision support content covering diagnostic and treatment algorithms
- Appointment of an NHS-selected group to review and approve the DSS content to ensure it is consistent and reflects commissioned pathways

6. Decision

Conclusion

This report highlights the significant potential for non-cancer stratified medicine to deliver benefit across the health ecosystem, and to the UK economy more broadly. There are several examples of stratified medicines in use in the NHS, and many more therapies with associated biomarkers in the development pipeline.

Cancer has been the exemplar, accounting for the majority of current and known future medicine-diagnostic combinations. However other therapeutic areas are catching up, notably cardiovascular, respiratory and infection amongst others. This creates an opportunity to learn from previous experiences in order to ensure that pitfalls are avoided and benefits are maximised to ensure that patients get access to innovative medicines faster.

Our survey results confirm that there is a great deal of anticipation and promise in this area for healthcare professionals, industry, payers, providers, patients and citizens. But there are also challenges to overcome, not least in terms of the magnitude of change that is required to transition into a new chapter of medicine.

The UK is uniquely placed to be in the vanguard of stratified medicine development given the investment in infrastructure, industry-academic collaborations and richness of available health data. Our series of recommendations will require collaboration and concerted action across a broad range of stakeholders if we are to deliver on the full promise of stratified medicine for patients.



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