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The benefits of personalised medicine to patients, society and healthcare systems

Final Report

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Glossary

Biomarker	A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease.
Diagnostic test	A type of test used to help diagnose a disease or condition.
DNA	A biological molecule that carries a person's genetic code.
Genomics	The study of the complete set of DNA (including all of its genes) in a person or other organism.
Genetic testing	The process of analysing cells or tissues to look for genetic changes that may be a sign of a disease or condition such as cancer.
Molecular diagnostics	A collection of techniques used to analyse biological markers in the genome and proteome – the individual's genetic code and how their cells express their genes as proteins – by applying molecular biology to medical testing.
Next-generation sequencing	An umbrella term used to describe a number of different modern DNA sequencing technologies that use a high-throughput method to determine a portion of the nucleotide sequence of an individual's genome.
Oncogene	A gene involved in normal cell growth, mutations of which are regularly associated with tumorigenic transformation.
PCR	Polymerase chain reaction. A procedure that produces millions of copies of a short segment of DNA through repeated cycles of: (1) denaturation, (2) annealing, and (3) elongation.
Protein expression	The production of proteins by cells. The study of protein expression in cancer cells may give information about a specific type of cancer, the best treatment to use, and how well a treatment works.
Germline mutation	A germline mutation, or germinal mutation, is any detectable variation within a germ cell (reproductive cell). A mutation in a sperm or oocyte, when they come together to form a zygote, is passed on to the offspring.
Gene expression profiling	In the field of molecular biology, gene expression profiling is the measurement of the activity of thousands of genes at once, to create a global picture of cellular function.

Abbreviations

ALK	anaplastic lymphoma kinase
AOTMiT	Agency for Health Technology Assessment and Tariff System
ATMPs	Advanced therapy medicinal products
CDF	Cancer Drug Fund
CEPS	Economic Committee for Health Products
CRC	Colorectal cancer
ctDNA	Circulating free tumour DNA
DNA	Deoxyribonucleic acid
DRG	Diagnosis-related group
EBE	European Biopharmaceutical Enterprises
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EQA	External Quality Assessment
EU	European Union
FH	Familial hypercholesterolemia
GEP	Gene expression profiling
HAS	National Authority for Health (France)
HER2	Human epidermal growth factor receptor 2
IHC	Immunohistochemistry
INCa	French National Cancer Institute
IQN Path	International Quality Network for Pathology
IVD	In vitro diagnostics
MA	Marketing authorisation
NCP	National cancer plan
NGS	Next-generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival

PCM	Polymerase chain reaction
PFS	Progression-free survival
PM	Personalised Medicine(s)
QALY	Quality-adjusted life-year
RR	Response rate
RWE	Real-world evidence
TKI	Tyrosine kinase inhibitors
WES	Whole exome sequencing
WGS	Whole genome sequencing

Executive summary

European Biopharmaceutical Enterprises (EBE) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) asked Charles River Associates to conduct an evidence-based analysis to (1) characterise the benefits of personalised medicine (PM) to patients, society and healthcare systems; (2) identify barriers and enablers to the development and adoption of PM in Europe; and (3) propose policy recommendations for decision-makers to overcome these barriers and incentivise the development and adoption of PM in Europe.

PM has been defined as any technology that aims to improve the prevention, diagnosis and treatment of diseases by using patients' individual characteristics to identify the most appropriate care. This is achieved through the use of (1) diagnostic technologies to stratify patients, (2) targeted therapies to act on specific biological features of an individual's disease, and (3) advanced medicines which are manufactured uniquely for an individual. PM includes both enabling technologies and treatment strategies, which enable personalisation through disease profiling, patient profiling, and novel therapies.


Project approach

In order to understand the benefits of PM, CRA first reviewed the existing literature on the value of PM. We adopted a case study approach that focuses on oncology, reflecting that this is the therapy area with the most examples to date. Four tumour types were selected – non-small cell lung cancer (NSCLC), breast cancer, ovarian cancer and melanoma – to identify different challenges associated with PM technologies. To understand the environment that encourages patient access to personalised medicine and their future development in terms of *enablers* and *barriers*, we selected five markets, including systems that have prioritised PM and those that have not, and different types of healthcare systems (Denmark, England, France, the Netherlands, and Poland). To complement our research, based on secondary sources, CRA also conducted a set of interviews with external stakeholders (four interviews for each of the five selected case study markets). The interviewees included oncologists, pathologists, payers, health policy advisors, and academics. The interviews focused on why access to PM varies across countries and the challenges for the future of PM.

The benefits of personalised medicine

The benefits of PM can be classified into three main categories: (1) delivering better treatments to patients, (2) delivering benefits to healthcare systems and society, (3) more efficient development of new medicines.

There is considerable evidence on the potential benefits for patients, clinicians, the healthcare system and the wider clinical development process in Europe today. For patients, this has resulted in greater likelihood of a clinical effect, a better outcome, and a reduced risk of adverse events. Although it is not always possible to quantify the specific impact from personalisation, according to the interviews the impact on patients in certain therapy areas has been significant.



Delivering better treatments to patients

- Improved efficacy i.e. patient more likely to receive a medicine delivering a clinical benefit
- Improvement in overall survival
- Reduced adverse events

Examples


An analysis of 570 phase II clinical trials showed that oncology PM therapies had **4X** the response rates compared to cytotoxic therapies ¹

One-year survival rates in women with stage 4 melanoma have increased from **36.1% in 2012 to 59.6% in 2014**, in parallel with the introduction of new PM for stage 4 melanoma ²

Studies evaluating severe to life-threatening adverse events in advanced urothelial carcinoma showed anti-PD-1 treatment reduced frequency of adverse events from **49.4% (with chemotherapy) to 15.0%** ³

Source: 1 – Schwaederle, M. et al. (2015); 2 – Public Health England; 3 – Bellmunt, J. et al. (2017)

The benefits to the healthcare system and society are evident from improvements in patient management and in terms of offsetting costs through reduced use of ineffective treatment, reduced cost of chronic conditions and reduced hospital stays.



Delivering benefits to healthcare systems and society

- Prevention and prediction of disease
- Improvement in patient management of diseases
- Prevents or delays more expensive care costs and allows scarce healthcare resources to be used most efficiently
- Reduces hospitalisation

Examples

Early identification of Familial Hypercholesterolemia (FH) through genetic testing has led to significant savings in healthcare costs – in the UK estimated savings to the NHS are **£6.9 million per year** ¹

Use of targeted therapy in NSCLC results in incremental savings to society per patient ranging from **€2,277 to €4,461**, primarily due to savings gained from productivity loss and remuneration received during sick leave ²


INCa concluded that an additional €1.7 million investment in regional genetics centres to support EGFR testing would save **€69 million** to French health insurance by identifying patients ³

On average, total costs were €602 lower for patients undergoing genetic testing with Oncotype Dx to guide chemotherapy decisions in breast cancer ⁴

Oncologists in the Netherlands estimate the mean hospital stay for PM is **3-4 days**, compared to more than a week for chemotherapy regimens ⁵

Source: 1 – Marks, D. et al. (2002); 2 – Lister, J. et al. (2012); 3 – Nowark, F. (2012); 4 – Katz, G. et al. (2015); 5 – Dutch medical oncologist interview

Finally, we have summarised the evidence on more efficient development of medicines. PM has improved the efficiency and effectiveness of running clinical trials. According to the interviews, these benefits are growing and will be even more significant in the future.



More efficient development of novel medicines

- More effective clinical trials
- Efficient clinical trials and reduction in cost
- More ethical clinical trials

Examples

The use of biomarkers raises the probability of success from phase 1 to approval from **8.5% to 25.9%** ¹

Subdivision of patients into genetic groups that dictate their responses to treatments results in smaller, more streamlined trials which could reduce development costs and rates of failure. However, this is as yet **unquantified** ²

PM products are more likely to be approved using phase II data – with smaller numbers of clinical trials participants. However, the requirements of value assessment and RWE mean potential benefits are as yet **unquantified** ³

Source: 1 – BIO (2016); 2 – OECD (2011); 3 – Vaidyanathan, G. (2012)

It is also clear that many stakeholders believe the benefits from PM will significantly increase in the near future as we move from an approach based on single-test to multi-target profiling and ultimately whole genome sequencing (WGS). For these benefits to be delivered, they argued, the environment needs to keep up with innovation.

The environment for personalised medicine

We have identified nine areas critical for the encouragement of PM and assessed the current performance of our five markets (as set out in Table 1 below). We find that Denmark and France have the markets that are most supportive to PM. These are countries that have prioritised PM, invested in testing infrastructure, and ensured that patients have access to both medicine and diagnostics (Dx). However, even in these markets, the environment is getting more challenging with changes to the funding of diagnostics (from a centralised to a hospital tariff based approach) and the introduction of a more formalised value assessment framework.































Table 1: The environment for PM in Europe

Environment for Personalised Medicines	DK	EN	FR	NL	PL
Policy prioritisation	●	●	●	●	●
Care environment	●	●	●	●	●
Diagnostic testing infrastructure	●	●	●	●	●
Uptake of diagnostics	●	●	●	●	●
Mechanism of value assessment	●	●	●	●	●
Use of real-world evidence	●	●	●	●	●
Speed of reimbursement	●	●	●	●	●
Speed of updating guidelines	●	●	●	●	●
Funding and investment	●	●	●	●	●

Source: CRA analysis

In England and the Netherlands, the picture is more mixed. In England, the integrated value assessment process has benefits, but this does not result in funding in practice. The fragmented reimbursement process for diagnostics is a significant barrier to uptake and is unsustainable given the trends towards profiling and next-generation sequencing (NGS). Finally, in Poland there are significant barriers to patients accessing PM. Looking across the five markets, we can identify a range of enablers and barriers to PM.

Figure 1: Summary of barriers and enablers to the adoption of PM in Europe

Barriers	Countries
Insufficient diagnostic testing capacity or poor quality labs limits use of novel tests	  
Delays or restricted reimbursement / access for novel personalised medicines	 
Lack of specific recognition of PM in value assessment guidelines	  
Delays to access and updating treatment guidelines to reflect innovative treatments	 
Limited level of physician exposure to current research and treatment trends	
Lack of inclusion of mutation testing in clinical guidelines	 
Restrictions on funding for specific high-priority therapy areas (particularly oncology) limits applicability beyond oncology	 
Funding availability or lack of clarity leading to insufficient funding of testing services	 
Enablers	Countries
Development of a specific plan or strategy on PM with dedicated investments in novel diagnostic technologies	  
Highly specialised and coordinated management of care (including testing infrastructure and expertise)	 
Availability of high quality testing platforms and technologies, supported by quality assessment protocols	
Inclusion of PM in guidelines promotes usage and reflects the development of clinical consensus to support PM	 
Early access schemes that favour PM	 
Clear funding and value assessment mechanisms for diagnostic products, and the alignment into the assessment of medicines	
Interim funding mechanisms that allow for outcomes-based managed entry agreements	 

The table above assesses the enablers and barriers today (and is inevitably somewhat backward looking) but it is clear from our interviews that the challenges introduced by PM are changing rapidly. In particular, the decoupling of medicines from companion diagnostics is underway. Countries are adopting broader panel-based approaches and genome sequencing. Where funding has been based on a diagnosis-related group (DRG)-based approach or reliant on the companies promoting PM to support testing, this is not sustainable going forward. It is challenging, particularly in markets such as England and Poland, but even in France, where funding has become less centralised. This situation will lead to significant additional challenges.

Conclusion and policy recommendations

Based on the above assessment of PM as well as input from the external interviews, we have developed a set of recommendations, addressed to policymakers, on what is needed to incentivise the development of PM in Europe and to improve equitable access to PM.

1. A coherent PM strategy is a key enabler to the uptake of personalised medicine. **A national policy to ensure prioritisation of PM should work hand in hand with existing health strategic plans** (e.g. National Cancer Plans). **The level of resources and funding needs to be aligned to aspirations.** A coherent PM strategy should articulate the genomic profiling strategy in terms whether to screen more patients using a broad targeted gene panels rather than fewer patients with whole genome assays.
2. **Continued emphasis is needed on better management of care, consolidating expertise and resources to ensure the adequate ‘personalisation of care’.** This can be achieved through a centralised approach (i.e. developing ‘centres of excellence’) or via cross-functional collaboration through healthcare networks. This will allow more coordinated management of the testing infrastructure and expertise.
3. **National governments should continue investing and cooperating in next-generation testing infrastructure (such as molecular genetics labs) as well as developing dedicated funding pathways to ensure access to diagnostics.** This can be facilitated through sharing best practices on how to fund different types of diagnostics and ensure high levels of access. Both centralised funding and a tariff-based approach have a role. The funding model must take into account the need for investment in infrastructure, as well as the need to encourage competition between diagnostic providers, and it must also be sustainable over the long term.
4. There is currently a lack of information on testing methods and a lack of clear data on diagnostic uptake, as well as poor oversight of the performance of labs. **Collecting data to track access to diagnostics (and making this public) as well as putting a greater emphasis on External Quality Assessments (EQA) of labs will help to ensure consistent testing quality throughout Europe and allow comparison between approaches.** This means promoting international platforms for EQA of labs and research into quality (e.g. IQN Path) to improve diagnostics testing and make EQA participation mandatory for labs across the EU. This should also promote consequences for poor performance of labs, e.g. report to a supervisory authority.
5. Tackling delays to reimbursement of new treatments will ensure more systematic and equitable access. **This can be improved by supporting better alignment of data requirements between regulators and health technology assessment (HTA) bodies to improve evidence development and facilitate the value assessment process.** Sharing best practices on HTA methodology for PM will contribute to finding a balance between the need for an integrated approach to assess the cost of diagnostics and medicines, and the need for a more flexible approach that incorporates new technologies (e.g. NGS). This should take into account the value of personalisation in their methodologies and should be pragmatic in using the available evidence. Interim/early access programmes can allow for early provision of innovative medicines while additional value assessment and pricing negotiations are being conducted.

1. Introduction

The European Biopharmaceutical Enterprises (EBE) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) asked Charles River Associates to conduct an evidence-based analysis to characterise the benefits of personalised medicine (PM) to patients, society and healthcare systems; to identify barriers and enablers to the development and adoption of PM in Europe; and to elaborate strategic recommendations for decision-makers to overcome these barriers and incentivise the development and adoption of PM in Europe.

1.1. Definition of personalised medicine

There is broad agreement that PM is a therapeutic strategy targeted to individual patients' or groups of patients' needs, ensuring that patients get the right treatment at the right time, using a combination of diagnostic and therapeutic tools. This sometimes means creating medicines uniquely for an individual patient, but it can also mean classifying individuals into stratified subpopulations that differ in their susceptibility to (or in the severity of) a particular disease or in their response to a specific treatment.¹

Various definitions of PM have been developed by industry, regulatory authorities, policymakers, clinicians, and researchers. In each case, the definition is intended to delineate a specific set of treatment approaches – including technologies needed to determine treatments (in particular diagnostic tests) as well as the treatments themselves – that are differentiated from other untargeted treatment approaches or therapeutic strategies.² Looking across a number of definitions, it is clear that 'personalised medicine' is used as a general term that often encompasses both technologies (i.e. specific medicines and associated devices) and treatment strategies (i.e. the design of an individualised treatment plan that matches a patient's specific characteristics).³

Taking into account definitions from EBE/EFPIA,⁴ the European Medicines Agency (EMA),⁵ the European Union (EU) Commission,⁶ the European Society for Medical Oncology (ESMO)⁷ and academia,⁸ the key features of PM are the following:

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- 1 EBE (2015) White paper on personalised medicine; see also ABPI (2009) The stratification of disease for personalised medicines Research driven recommendations to strengthen a unified UK strategy through a stakeholder alliance
 - 2 EMA (2017) Concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle
 - 3 It is also often used interchangeably with "targeted", "precision", "stratified" medicines
 - 4 EBE website. Available at: <http://www.ebe-biopharma.eu/personalised-medicine/>
 - 5 EMA website. Available at:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/03/news_detail_002705.jsp&mid=WC0b01ac058004d5c1
 - 6 EU commission. Workshop on personalised medicines: role of patients, consumers and healthcare professionals (2017), available at:
http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2017/05/WC500227976.pdf
 - 7 ESMO Personalised Cancer Medicine Factsheet, available at:
<http://www.esmo.org/content/download/34303/682038/file/ESMO-Personalised-Cancer-Medicine-Fact-Sheet.pdf>
 - 8 Schleidgen, S., Klingler, C., Bertram, T., Rogowski, W. H. and Marckmann, G. (2013). What is personalized medicine: sharpening a vague term based on a systematic literature review. *BMC medical ethics*, 14(1): 55.

- Targeted: Treatments are expected to vary between individuals with the same disease.
- A range of technologies are incorporated: There are a range of medical technologies that can deliver benefits – small molecule, large molecule (biologics), advanced therapy medicinal products (ATMPs).
- Diagnostic testing is involved: Personalisation requires additional information about the patient or the nature of the disease, obtained via diagnostic testing that uses technologies such as molecular diagnostics, gene sequencing (e.g. next generation sequencing) or immunohistochemistry assays.

Based on the information above, we define PM as any technology that aims to improve the prevention, diagnosis and treatment of diseases by using patients' individual characteristics to identify the most appropriate care. In terms of treatment, this can broadly be classified into two categories:

- Targeted therapies: These are therapies that act on specific molecular targets associated with a disease. These targets can arise from specific mutations associated with the disease or they can be protein-expression targets within biological pathways. In oncology, for example, targeted therapies exert anticancer effects through multiple mechanisms: cell proliferation inhibition, apoptosis induction, metastasis suppression, and immune function regulation.⁹
- Individualised therapies: These include modified T-cell therapies and gene therapies, which are considered ATMPs.¹⁰ The technologies are specifically targeted at an individual patient, which uses the patient's own cells), or are produced from donor cells. These are intended for use within the approved indication for the product.¹¹

In terms of diagnosis, PM refers to a process by which genetic information is used to evaluate patients at risk of developing particular diseases, or who have mutations which can be targeted by specific medicines. This includes next generation sequencing (NGS), assays for specific mutations, and gene expression profiles that characterise sections of an individual's genome.¹²

The evolution of genomic technologies

Until recently, the application of PM has been associated with companion diagnostics based on identifying a single biomarker. More recent progress in PM can be attributed to technological advances in sequencing, particularly in cancer, enabling more routine genomic study of tumours in clinical management.¹³ NGS approaches vary: from small gene panels that sequence only "hotspots" of mutation (regions of DNA that have a high

⁹ Ke, X. and Shen, L. (2017). Molecular targeted therapy of cancer: The progress and future prospect. *Frontiers in Laboratory Medicine*, 1(2): 69-75.

¹⁰ EMA. Advanced therapy medicinal products
¹¹ Brake B. and Ganan Jimenez A. Advanced Therapy Medicinal Products (2011) – European Experience and Challenges – European Medicines Agency – ASEAN training. Kuala Lumpur. 31 May 2011

¹² Van't Veer, L. J., Dai, H., Van De Vijver, M. J., He, Y. D., Hart, A. A., Mao, M., ... and Schreiber, G. J. (2002). Gene expression profiling predicts clinical outcome of breast cancer. *Nature*, 415(6871): 530-536.

¹³ Hyman, D. M., Taylor, B. S. and Baselga, J. (2017). Implementing genome-driven oncology. *Cell*, 168(4): 584-599.

propensity to mutate), to targeted gene panels typically sequencing the entire coding regions of 50–500 genes, to whole exome sequencing (WES) and whole genome sequencing (WGS). Table 2 shows the evolution of NGS technology in precision medicine from smaller hotspot panel testing to larger panel and WGS.

Table 2: Evolution of NGS technology in personalised medicine

NGS technology	Description
Hotspot panels	A collection of frequently mutated hotspots that are either clinically actionable or have diagnostic/prognostic significance
Actionable gene panels	The entire coding region of targeted genes, so that other pathogenic mutations outside frequently mutated sites can be interrogated
Disease-focused Panels	Genes for a particular disease; largely used for germline mutations to screen for the risk of inherited diseases, or to diagnose genetic diseases
Comprehensive panels	Disease-associated regions of the exome with high analytical sensitivity and specificity
Whole exome sequencing (WES)	The complete coding region of the genome. Estimated to encompass only approximately 1-2% of the genome, yet contains approximately 85% of disease-causing pathogenic variants
Whole genome sequencing (WGS)	The most comprehensive tool for future clinical application, WGS is expected to provide full coverage of all protein coding regions like WES as well as intronic and other non-coding DNA regions associated with inherited diseases

Source: CRA analysis of Dong (2015)¹⁴

As the relationship between sequence variation and disease management becomes better understood, use of genetics (the analysis of genes and gene modification) and genomics (the analysis of gene expression) in the diagnosis and management of a patient's condition will become increasingly relevant in the clinical setting.¹⁵

1.2. Methodology

To investigate the benefits of PM, as well as the barriers and enablers to its use, we have adopted a three-step methodology:

- A literature review on the definition of PM, its benefits, and its enablers and barriers in Europe

¹⁴ Dong, L., Wang, W., Li, A., Kansal, R., Chen, Y., Chen, H. and Li, X. (2015). Clinical Next Generation Sequencing for Precision Medicine in Cancer. *Current Genomics*, 16(4): 253–263. <http://doi.org/10.2174/1389202915666150511205313>

¹⁵ Gaff, C. L., Winship, I., Forrest, S., Hansen, D., Clark, J., Waring, P., ... and Sinclair, A. (2017). Preparing for genomic medicine: a real world demonstration of health system change. *NPJ genomic medicine*, 2(1): 16.

- The development of four therapeutic case studies
- An external interview programme to validate findings from the literature review and to gather stakeholder opinion.

Literature review

The first step was to review the literature on the value of PM. CRA began by collecting papers from EBE/EFPIA member companies and previous analyses.¹⁶ We then turned to the growing literature of published journal papers, government reports and public policy documents from stakeholders on the added value of different types of PM. As listed in Table 3 below, we also reviewed reports/articles assessing the challenges associated with PM. We searched PubMed using the keywords ‘personalised medicine’, ‘targeted medicine’, ‘stratified medicines’, ‘companion diagnostics’, ‘value’, ‘enablers’ and ‘barriers’.

Table 3: Literature review

Type	Number	Examples
Academic articles	133	<ul style="list-style-type: none"> • An economic perspective on personalised medicine (Jakka, S. and Rossbach, M., 2013) • Implementing genome-driven oncology (Hyman, D.M., Taylor, B.S. and Baselga, J., 2017) • Systematic review of the clinical and economic value of gene expression profiles for invasive early breast cancer available in Europe (Blok, E.J. et al, 2018)
Industry published or commissioned reports	7	<ul style="list-style-type: none"> • EBE White Paper on Personalised Medicine • EuropaBio’s paper on PM • PhRMA Value of Personalised medicine • Office of Health Economics Report on Gene Therapy (2016) • IHE Access to innovative medicines analysis (2016)
Public agency reports	9	<ul style="list-style-type: none"> • National Health Service (NHS) England ‘Improving outcomes through personalised medicine’ • European Commission report ‘omics in PM’ • French National Cancer Plan 2017–2020

Source: CRA analysis

CRA also captured the perspective of EBE/EFPIA experts through a series of nine structured interviews with EBE/EFPIA member companies on the evolution of technologies and the benefits of PM. The objective of these interviews was to understand the perspective of different types of company (in terms of size and focus on different technologies) and to obtain guidance on the selection of therapy areas that we could use

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The 2014 EBE White Paper on Personalised Medicine but also the white paper on PM developed by EuropaBio and the ABPI white paper on “Stratified medicine in the NHS”.

as case studies. Lastly it also helped us understand how future technologies are likely to introduce new challenges.

Development of case studies

The next step was to undertake a fact-based landscape analysis of the environment for PM in Europe. To do this we developed a set of therapeutic case studies.

The selection of case studies was based on input from EBE/EFPIA member companies and focused on where PM have successfully been brought to market in Europe over the past decade. The aim was to select examples that have a mix of established and more recently launched PM, but also a mix of technology types (mix of complementary and companion diagnostics, including technologies across oncogenetic testing, molecular diagnostics, and genetic risk-profiling).

Whilst gene/cell therapies are important types of PM, their limited commercialisation at this time makes it difficult to assess their experience in the real world or to draw conclusions on their benefits.¹⁷ As a result, cell and gene therapies, as well as strategies for tailoring treatments to individual patients, are not included in this analysis.

After reviewing a range of options, we agreed to focus the case studies only in oncology, reflecting that this is the therapy area with the most examples to date.¹⁸ Based on the above criteria, four tumour types were selected as cases studies (see Figure 2). Evidence from other therapy areas has been included but only to the extent this is included in the literature review.

Figure 2: Selected case study products

	Non-small cell lung cancer (NSCLC)	Breast cancer	Ovarian cancer	Melanoma
Products / targets	<ul style="list-style-type: none"> Multiple specific mutations (ALK+, ROS+, EGFR) plus protein-expression targets (PD1) Novel diagnostic approaches (e.g. ctDNA testing) 	<ul style="list-style-type: none"> Germline and somatic mutation-targeted therapies Potential usage of advanced diagnostics (e.g. Oncotype) separate from treatments 	<ul style="list-style-type: none"> Introduction of PARP inhibitors Use of diagnostics in screening programs for BRCA mutations 	<ul style="list-style-type: none"> Introduction of BRAF inhibitors (and later BRAF / MEK inhibitors) Use of tumour mutation testing for treatment decision-making

Source: CRA analysis

To investigate the environment for each case study, we also needed to choose a subset of European markets to examine in detail. The aim was to include countries with different types of healthcare systems in order to understand how the funding and delivery of care affects the adoption of PM. From a policy study perspective, we established four criteria to consider for country selection:

1. Countries should represent different regions of Europe.
2. Countries should represent different reimbursement mechanisms and approaches to health technology assessment (HTA) (system based on relative or cost-effectiveness, recognition of the value of targeting).
3. Countries should have some level of policy activity and prioritisation for PM.

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¹⁷ In addition, EBE/EFPIA is undertaking a separate study specifically focused on this area.

¹⁸ We note that other therapy areas can be personalised (e.g. recent launches for cystic fibrosis targeting specific CFTR mutations), but oncology was identified as the area in which personalised medicines were most established.

4. Countries should have sufficient treatment infrastructure to enable adoption of innovative oncology products.

Using these criteria, we assessed different European countries. This analysis led us to choose five case study markets as listed in Table 4. It should be noted that case studies were chosen to learn about the use of PM, the benefits it has delivered and the barriers and enablers; they were not intended to be representative of Europe, and we take this into account in the policy recommendations.

Table 4: Case study market selection

Country	Rationale for country selection based on preliminary research
France 	<ul style="list-style-type: none"> • Large western European market • High PM prioritisation – key focus area within national cancer plan and recent PM plan ‘Genomic Medicine 2025’
England 	<ul style="list-style-type: none"> • Large western European market • High PM prioritisation – the Government has released a strategy on genomics and PM • Often seen as restrictive due to formal HTA process
Denmark 	<ul style="list-style-type: none"> • Northern European market • High PM prioritisation – Danish Government has implemented the ‘National Strategy for Personalised Medicine 2017–2020’ • Identified as having developed PM infrastructure
The Netherlands 	<ul style="list-style-type: none"> • Large northern European market • Good policy prioritisation on PM – PM included in health/research agenda • Identified as having developed PM infrastructure
Poland 	<ul style="list-style-type: none"> • Large eastern European market • No evidence of any policy prioritisation for PM • Limited PM infrastructure

For each market we examined the existing framework (market regulation and dynamics in EU Member States) and identified the constraints facing different types of PM innovations in selected countries in the light of the evolving market dynamics for such products.

External interviews

To complement the above research, CRA conducted a set of interviews with external stakeholders in order to support the analysis of the benefits of personalised oncology medicines in each market. These interviews were intended to fill evidence gaps from the literature review but also to gather the perspective of different types of stakeholders including policymakers, patient groups and academics on why access to PM varies across countries.

CRA conducted 19 interviews – 4 for each of the 5 selected case study markets (only 3 for Denmark). We focused on stakeholders relevant to market access and evaluation in each market.¹⁹

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Interviews were conducted from 10 January to 15 February 2018. Interviews were blind and were conducted either in English or in the local language. A number of follow-up interviews focused on the challenges of future approaches to diagnostic testing.

Table 5: External interviews conducted by CRA in each of the five markets

Country	Stakeholder type	Organisation
Denmark	Pathologist	Danish pathologist organisation
	Payer	Local payer (hospital level)
	Hospital oncologist	Specialist cancer hospital
England	Payer	NHS England
	Payer	National Institute for Health and Care Excellence (NICE) advisor
	Hospital oncologist	Specialist cancer hospital
	Pathologist	International Quality Network for Pathology (IQN Path)
France	Payer/oncologist	Payer/oncologist Economic Committee for Health Products (CEPS)
	Payer/oncologist	Payer/oncologist French National Authority for Health – Transparency Commission (HAS CT)
	Hospital oncologist	Hospital Fayette
	Pathologist/academic	French Society of Pathology
The Netherlands	Payer	Current advisor/former National Health Care Institute (ZIN) payer
	Payer	National health policy advisor
	Pathologist/academic	European Society of Pathology
	Hospital oncologist	Specialist cancer hospital
Poland	Payer	National Health Fund advisor (former)
	Payer	Agency for Health Technology Assessment and Tariff System (AOTMiT) advisor (former)
	Pathologist	Maria Skłodowska Curie Institute
	Hospital oncologist	Specialist cancer hospital

1.3. Structure of this report

The structure of this report is as follows:

- Chapter 2 examines the existing evidence of the value of PM, using evidence from the literature review and the case studies in breast cancer, non-small cell lung cancer (NSCLC), ovarian cancer and melanoma.
- Chapter 3 considers the factors affecting the environment for PM and barriers and enablers to the use of PM in the five countries.
- Chapter 4 presents our conclusions and sets out the policy implications.

2. The benefits of personalised medicine

In this chapter we review the evidence on the value of PM. We start with the general literature. The extent to which the theoretical benefits can be observed has been discussed extensively in reports by the European Commission,²⁰ scientific literature, and reports from national government, industry^{21,22,23} or other institutions.^{24,25} We also incorporate evidence from our four therapeutic case studies (breast cancer, NSCLC, melanoma and ovarian cancer). We have identified three main categories of benefits:

- 1) Better treatments for patients
- 2) Delivering benefits to healthcare systems and society
- 3) More efficient development of novel medicines

Although the focus is on Europe, we also report key international evidence where relevant.

2.1. Better treatments for patients

The development of PM could bring benefits to patients in a number of ways:

- Improved efficacy: patient more likely to receive a medicine delivering a clinical benefit, and treatment targeted at patients who will respond
- Improvements in overall survival
- Reduced adverse events: PM could be targeted at patients who are less likely to have an adverse reaction, reducing safety concerns

2.1.1. Improve efficacy through targeted response rate

As described in the European Commission paper,²⁶ PM offers the opportunity to have a higher probability of desired outcomes for each treated patient thanks to better-targeted therapies and earlier disease intervention than has been possible in the past.

This means moving away from ‘trial-and-error’ prescribing to initial prescription of optimal therapies.²⁷ For example, with untargeted therapies around 38% of patients with depression, 50% of arthritis patients, 40% of asthma patients, and 43% of diabetic

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- 20 European Commission (2013). Use of ‘-omics’ technologies in the development of personalised medicine, Commission staff working document, Brussels, 25.10.2016; SWD(2013) 436 final
- 21 The 2014 EBE White Paper on Personalised Medicine but also the white paper on PM developed by EuropaBio or the ABPI white paper on “Stratified medicine in the NHS”.
- 22 Kievits, T., Niese, D., Hansen, L. T. and Collins, P. (2012). Personalised medicine: status quo and challenges. Sarah Lee Ketner. Europa Bio.
- 23 PhRMA (2015) Chart Pack: Value of Personalized medicines – spring 2015.
- 24 Jakka, S. and Rossbach, M. (2013). An economic perspective on personalized medicine. *The HUGO Journal*, 7(1)
- 25 European Parliament (2015) Briefing: Personalised medicine The right treatment for the right person at the right time – October 2015
- 26 European Commission (2013). Use of ‘-omics’ technologies in the development of personalised medicine, Commission staff working document, Brussels, 25.10.2016; SWD(2013) 436 final
- 27 NHS England (2016). Improving outcomes through personalised medicine. Available at: <https://www.england.nhs.uk/wp-content/uploads/2016/09/improving-outcomes-personalised-medicine.pdf>

patients were not responding to initial treatment.²⁸ By learning more about which molecular variations best predict how a patient will respond to a treatment, physicians will have more information to guide their decision about which medications are likely to work best.

The use of genetic and other forms of molecular screening could help predict the best dosing schedule or combination of medicines for a particular patient. This offers the potential to improve healthcare provision by better matching patient needs and therapeutic benefits, and through a more informed choice of therapy.²⁹ Genetic information can distinguish between patients who are likely to respond strongly to pharmacologic treatment and those who will receive no benefit.

Genetic testing is becoming widely used to evaluate which medicines may work best for cancer treatment. There are several examples of this in common practise:

- In metastatic colon cancer, it is known that approximately 40% of patients are unlikely to respond to cetuximab and panitumumab because their tumours have a mutated form of the KRAS gene.³⁰
- In breast cancer, about 30% of cases are characterised by overexpression of a cell surface protein called human epidermal growth factor receptor 2 (HER2).³¹ There are now several HER2 targeted treatments (Table 6).
- In NSCLC, new anti-PD-1 immunotherapy, in addition to a standard chemotherapy regimen, has makes it only half as likely that previously untreated patients would die, meaning that at the end of 21 months, an extra 2 patients out of every 10 are still alive.³²

Among all breast cancer subtypes, HER2-positive (HER2+) advanced breast cancer has seen the most progress in its treatment over the last decade.³³ As illustrated in Table 6, the successful development of trastuzumab, the first medicine targeting HER2-positive cancer, validated the concept that disease biology can be improved by treating the underlying molecular driver. In the past decade, three more HER2-directed therapies – lapatinib, pertuzumab, and T-DM1 – have earned regulatory approval based on data in the metastatic and early stage settings progressively offering greater survival benefits.³⁴

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- 28 Personalised Medicine Coalition. The Case for Personalised Medicine. 2014.
- 29 ABPI (2014). Stratified medicine in the NHS: An assessment of the current landscape and implementation challenges for non-cancer applications. Available at: http://www.abpi.org.uk/our-work/library/medical-disease/Documents/stratified_med_nhs.pdf
- 30 Tan, C. and Du, X. (2012). KRAS mutation testing in metastatic colorectal cancer. *World Journal of Gastroenterology : WJG*, 18(37): 5171–5180. <http://doi.org/10.3748/wjg.v18.i37.5171>
- 31 Personalised Medicine Coalition. The Case for Personalised Medicine. 2014.
- 32 Gandhi, L. et al. (2018) Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer, *New England Journal of Medicine*
- 33 Cardoso, F., Costa, A., Senkus, E., Aapro, M., André, F., Barrios, C. H., ... Winer, E. (2017). 3rd ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). *Annals of Oncology*, 28(1): 16–33. <http://doi.org/10.1093/annonc/mdw544>
- 34 DrakakiA, Hurvitz,SA. HER2-Positive Breast Cancer: Update on New and Emerging Agents. *American journal of hematology/oncology*, 2015; 11 (4): 17-23.

Table 6: Overview of treatments approved for HER2+ breast cancer

Product	EMA approval date	Median survival ³⁵	Description
Trastuzumab	April 2006 (August 2000 ³⁶)	12.8 months	HER2 / HER3 inhibitor
Lapatinib	June 2008	17 months	Dual tyrosine kinase inhibitors (TKI) targeting HER2 and epidermal growth factor receptor (EGFR)
Pertuzumab	March 2013	Not reached (>37.6 months)	HER2-targeted inhibitor (complementary to trastuzumab) ³⁷
Ado-trastuzumab emtansine (T-DM1)	November 2013	30.9 months	Anti-HER2 antibody-drug conjugate

Source: CRA analysis

DNA enrichment and sequencing technologies have matured to the point where they can now generate reliable results on individual tumours within clinically meaningful time frames using small amounts of tumour tissue. This is clearly beneficial to the patients who have been identified as responders, those whose likelihood of responding is higher. It is also valuable for non-responders, as they can be offered alternative approaches more quickly (rather than having to wait until it is observed they are not responding to treatment).³⁸

2.1.2. Improvements in overall survival

The identification of the molecular drivers of specific tumours has enabled therapies to be targeted to an individual's disease. In fact, the development of new personalised cancer treatment options has outpaced that for all other disease types, and continues to accelerate.

The impact of PM in diverse cancers was analysed in a meta-analysis of phase II clinical trials (570 studies; 32,149 patients), comparing response rate (RR), progression-free survival (PFS) and overall survival (OS) in the arms of a clinical trial (group of patients receiving a specific treatment) that used a personalised strategy versus the arms which

³⁵ Median survival taken from initial authorisation EPAR scientific discussion, available on www.ema.europa.eu
³⁶ Although initially approved in August 2000, central EMEA authorisation for breast cancer and subsequent commercialisation dates from 2006.
³⁷ Nahta, R., Hung, M. C. and Esteva, F. J. The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. *Cancer Res.* 2004;64:2343-2246.
³⁸ Cornetta, K. and Brown, C. G. (2013). Perspective: balancing personalized medicine and personalized care. *Academic medicine: journal of the Association of American Medical Colleges*, 88(3): 309.

did not.³⁹ This showed that PM had higher response rates.⁴⁰ Non-personalised targeted arms had poorer outcomes compared with personalised targeted therapy.

Prior to advent of PM, the treatment options for breast cancer were not tailored to the conditions of particular patients and had significant side effects. Adjuvant treatment was shown to result in an approximately 50% reduction in recurrence of the disease after a median follow-up of 1 – 2.4 years' treatment in patients with HER2-positive disease.⁴¹ The contribution of personalised medicine to improvement in mortality is well documented, although it is not possible to estimate the amount of its contribution.⁴² Mortality in the EU overall has improved from 17.9/100,000 in 2002 to 15.2/100,000 in 2012, and is predicted to fall further to 13.4/100,000 by 2020.⁴³ Although it is impossible to attribute a proportion of the increase to PM, looking across European markets, age adjusted five-year survival rates have continued to increase.

In England, five-year age-standardised net survival for breast cancer in women has increased from 71% in 1990–1999 to 87% in 2010–2011, with the greatest increase following the introduction of targeted therapies. Overall, almost 8 in 10 women diagnosed with breast cancer today are predicted to survive their disease for at least ten years.⁴⁴ Further, the Office for National Statistics in the UK has showed that one-year age-sex-standardised survival for patients diagnosed with lung cancer increased from 25.7% in 2000 to 40.7% in 2015.⁴⁵ The improvements in outcomes illustrated by survival statistics (which necessarily are a lagging indicator) are echoed by the experiences of oncologists and health system stakeholders.⁴⁶ Alongside improvements in screening to identify early disease, oncologists strongly link the availability of targeted HER2 treatments to improvements in clinical outcomes. In addition, payers see the evolution of HER2+ treatment, beginning with Herceptin, as a 'watershed' for improving cancer survival and patient outcomes.

The treatment landscape for metastatic melanoma has also shifted dramatically over a short period of time. This is primarily due to the discovery of oncogenic mutations in the genes controlling the MAP kinase pathway (the proteins chain in the cell that communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell). This enables the rapid development of targeted medicines for

39 Schwaederle, M., Zhao, M., Lee, J. J. et al. Impact of Precision Medicine in Diverse Cancers: A Meta-Analysis of Phase II Clinical Trials. *J Clin Oncol*. 2015;33(32):3817-3825

40 The observed outcomes were a mean RR was 6.2% and 29.2%, respectively; median PFS of 2.8 months and 6.8 months, respectively; and median OS of 9 months and 15.9, respectively.

41 Piccart, M. First results from the HERA trial. Presented at the annual meeting of the American Society of Clinical Oncology 2005. www.asco.org/ac/1,1003,_12-002511-00_18-0034-00_19-005816-00_21-001,00.asp

42 "The Right Treatment for the Right Patient – Personalised Treatment of Breast Cancer" A. Scharl, T. Kühn, T. Papatthemelis and A. Salterberg, *Geburtshilfe Frauenheilkd*. 2015 Jul; 75(7): 683–691. doi: 10.1055/s-0035-1546270

43 Carioli, G., Malvezzi, M., Rodriguez, T., Bertuccio, P., Negri, E. and La Vecchia, C. (2017). Trends and predictions to 2020 in breast cancer mortality in Europe. *The Breast*, 36, 89-95.

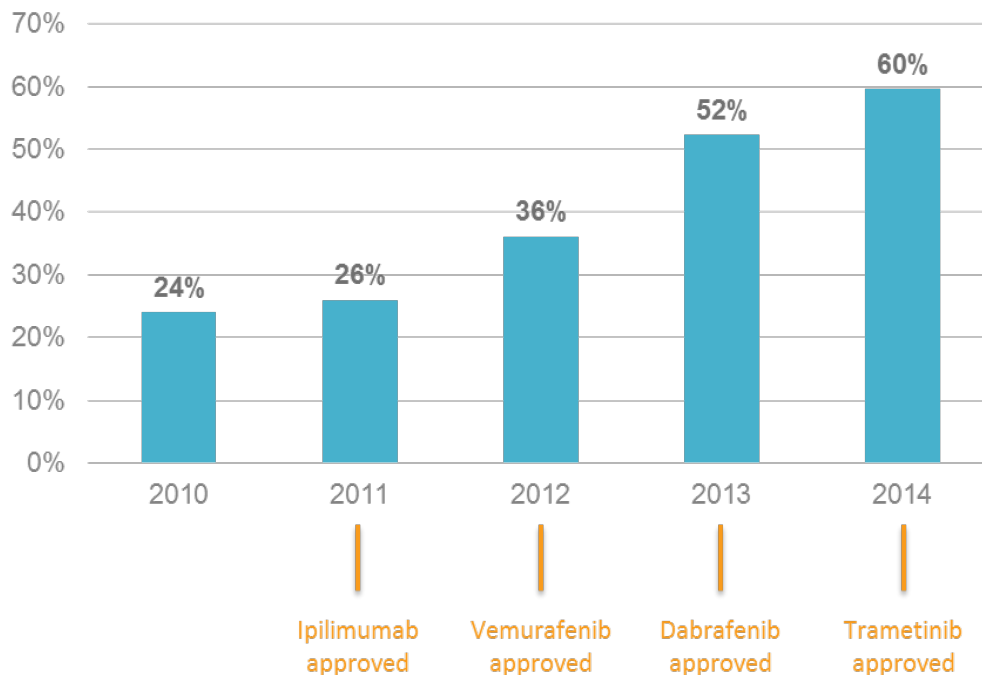
44 Cancer Research UK – Breast Cancer (C50), Age-Standardised Ten-Year Net Survival, Women (Aged 15-99), England and Wales, 1971-2011 – Data were provided by London School of Hygiene and Tropical Medicine on request, 2014.

45 Office for National Statistics (2017). Index of cancer survival for Clinical Commissioning Groups in England: adults diagnosed 2000 to 2015 and followed up to 2016

46 Interviews with oncologists and payers

melanoma.⁴⁷ Looking again at data from the UK, Public Health England shows that one-year survival rates in women with stage 4 melanoma have increased from 24% 2010 to 60% in 2014, in parallel with the introduction of new personalised treatments for stage 4 melanoma (see Figure 3). Alongside the introduction of immunotherapies (CTLA4-targeting and PD1-targeting), the combination BRAF/MEK inhibitors (medicines such as dabrafenib and trametinib) are cited by oncologists as driving improvements in melanoma survival.⁴⁸

Figure 3: One-year survival rate for melanoma, by stage, in adult women (2012–2014)



Source: Public Health England

2.1.3. Reduced adverse events

The use of genetic markers to facilitate safer and more effective dosing regimens and selection of patients can reduce the likelihood of adverse events. Several authors have argued that pharmacogenomics can play a role in identifying drug responders and non-responders, as well as avoiding adverse drug reactions and optimising drug dosing based on the individual.⁴⁹ A meta-analysis evaluating grade 3 to 4 adverse events (severe to life-threatening) in advanced melanoma treatment, anti-PD1 treatment resulted in fewer

⁴⁷ Lindsay, C, Spiliopoulou, P, Waterston, A. (2015). Blinded by the light: Why the treatment of metastatic melanoma has created a new paradigm for the treatment of cancer. *Ther Adv Med Oncol*, 7. <https://dx.doi.org/10.1177%2F1758834014566619>

⁴⁸ Interviews with Oncologist KOLs

⁴⁹ Chun-Yu Wei, Ming-Ta Michael Lee, Yuan-Tsong Chen (2012). Pharmacogenomics of adverse drug reactions: implementing personalised medicine. *Human Molecular Genetics*, Volume 21, Issue R1, 15 October 2012, Pages R58–R65, <https://doi.org/10.1093/hmg/dds341>

treatment-related adverse events compared to chemotherapy.⁵⁰ Similarly, in advanced urothelial carcinoma, one study showed that using pembrolizumab instead of chemotherapy reduced the frequency of adverse events from 49.4% to just 15.0%.⁵¹

Additional data can be found in areas other than cancer. One example of this is abacavir, a nucleoside analogue reverse transcriptase inhibitor (NRTI) used as a first-line treatment for HIV. The main undesirable effect of abacavir is hypersensitivity, affecting about 1 in 17, which in rare cases can be fatal. A genetic test can indicate a patient's predisposition to hypersensitivity, thereby allowing doctors to avoid adverse events by pursuing alternative therapeutic options.⁵² This has significantly reduced the pressure on health services that previously had to deal with patients who only found out they were allergic after they started taking the medicine.⁵³

Some authors have argued that PM means that patients will become more involved in decisions about their own treatment plan, increasingly discussing therapeutic options and their consequences with their doctors. Patient non-compliance with treatment leads to adverse health effects and increased overall healthcare costs. It has been suggested that when personalised therapies prove more effective or present fewer side effects, patients may be more likely to comply with their treatments.⁵⁴ There is no empirical data on this yet, but the greatest impact might be to come, as PM is applied to the treatment of chronic conditions such as cardiovascular disease⁵⁵ and diabetes,⁵⁶ in which non-compliance commonly exacerbates the severity.

2.1.4. Summary

Evidence that PM delivers better treatment outcomes for patients is summarised below.

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- 50 Hao, C., Tian, J., Liu, H., Li, F., Niu, H. and Zhu, B. (2017). Efficacy and safety of anti-PD-1 and anti-PD-1
combined with anti-CTLA-4 immunotherapy to advanced melanoma: A systematic review and meta-analysis of
randomized controlled trials. *Medicine*, 96(26).
- 51 Bellmunt, J., De Wit, R., Vaughn, D. J., Fradet, Y., Lee, J. L., Fong, L., ... and Necchi, A. (2017). Pembrolizumab
as second-line therapy for advanced urothelial carcinoma. *New England Journal of Medicine*, 376(11): 1015-
1026.
- 52 ABPI (2014). Stratified medicine in the NHS: An assessment of the current landscape and implementation
challenges for non-cancer applications. Available at: [http://www.abpi.org.uk/our-work/library/medical-
disease/Documents/stratified_med_nhs.pdf](http://www.abpi.org.uk/our-work/library/medical-disease/Documents/stratified_med_nhs.pdf)
- 53 NHS England (2016). Improving outcomes through personalised medicine. Available at:
<https://www.england.nhs.uk/wp-content/uploads/2016/09/improving-outcomes-personalised-medicine.pdf>
- 54 Personalised Medicine Coalition. The Case for Personalised Medicine. 2014.
- 55 Umans-Eckenhausen, M. A., Defesche, J. C., van Dam, M. J. et al. Long-term compliance with lipid-lowering
medication after genetic screening for familial hypercholesterolemia. *Arch Intern Med*. 2003; 163(1):658.
- 56 NHS England (2016). Improving outcomes through personalised medicine. Available at:
<https://www.england.nhs.uk/wp-content/uploads/2016/09/improving-outcomes-personalised-medicine.pdf>

Table 7: The impact of personalised medicine on delivering better treatments for patients

Type of impact	Key findings
Targeted and personalised intervention that identifies patients most likely to respond	<ul style="list-style-type: none"> Tumour profiling in metastatic colon cancer has shown that approximately 40% of patients are unlikely to respond to cetuximab and panitumumab because their tumours have a mutated form of the KRAS gene.⁵⁷ A meta-analysis of phase II clinical trials (570 studies; 32,149 patients) showed that oncology PM therapies had higher response rates than cytotoxic therapies.⁵⁸
Better outcomes – improvement in overall survival	<ul style="list-style-type: none"> Adjuvant treatment was shown to result in an approximately 50% reduction in recurrence of the disease after a median follow-up of 1–2.4 years' treatment in patients with HER2+ breast cancer.⁵⁹ With the introduction of new personalised treatments for stage 4 melanoma, one-year survival rates in women with stage 4 melanoma have increased from 36.1% 2012 to 59.6% in 2014. In NSCLC, new anti-PD-1 immunotherapy in addition to a standard chemotherapy regimen has makes it only half as likely that a previously untreated patient will die.⁶⁰
Better outcomes – reduced adverse events	<ul style="list-style-type: none"> In advanced urothelial carcinoma, pemprolizumab with chemotherapy has reduced the frequency of adverse events from 49.4% to 15.0%.⁶¹ In a HIV treatment, a genetic test can avoid adverse events by indicating the need for alternative therapeutic options.⁶²

Source: CRA analysis

2.2. Delivering benefits to the healthcare system and to society

PM has the potential to change the way healthcare professionals and systems identify and manage health problems.⁶³ This can begin with improved diagnoses and treatments

57 Tan, C. and Du, X. (2012). KRAS mutation testing in metastatic colorectal cancer. *World Journal of Gastroenterology: WJG*, 18(37): 5171–5180. <http://doi.org/10.3748/wjg.v18.i37.5171>

58 Schwaederle, M., Zhao, M., Lee, J. J. et al. Impact of Precision Medicine in Diverse Cancers: A Meta-Analysis of Phase II Clinical Trials. *J Clin Oncol*. 2015;33(32):3817-3825

59 Piccart, M. First results from the HERA trial. Presented at the annual meeting of the American Society of Clinical Oncology 2005. www.asco.org/ac/1,1003,_12-002511-00_18-0034-00_19-005816-00_21-001,00.asp

60 Gandhi, L. et al. (2018) Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer, *New England Journal of Medicine*

61 Bellmunt, J., De Wit, R., Vaughn, D. J., Fradet, Y., Lee, J. L., Fong, L., ... and Necchi, A. (2017). Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *New England Journal of Medicine*, 376(11): 1015-1026.

62 Chun-Yu Wei, Ming-Ta Michael Lee, Yuan-Tsong Chen (2012). Pharmacogenomics of adverse drug reactions: implementing personalised medicine. *Human Molecular Genetics*, Volume 21, Issue R1, 15 October 2012, Pages R58–R65, <https://doi.org/10.1093/hmg/dd341>

due to better matching of patients' needs and therapeutic benefits, and can ultimately lead to more efficient allocation of healthcare resources. Theoretically, these can occur in a number of ways:

- Focusing on prevention and prediction of disease
- Improving the management of diseases
- Preventing or delaying more expensive care costs and allowing scarce healthcare resources to be used most efficiently.

According to research, fewer unnecessary interventions alongside improved outcomes are key drivers for payers to provide access to novel diagnostic tests that support implementation of PM.⁶⁴

2.2.1. Focusing on prevention and prediction of disease

One of the promises of PM is to preserve individual health in people with high risk by starting early treatment or prevention protocols. This has the potential to lower overall healthcare costs through early detection, prevention, accurate risk assessments and efficiencies in care delivery.⁶⁵

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. Thus PM could be said to shift the emphasis in treatment from reaction to prevention.⁶⁶ 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 or delay onset or reduce impact.⁶⁷ One example of this can be found in familial hypercholesterolemia (FH), which causes raised cholesterol and a significant risk of heart attack and other cardiac events in the under 50s. It affects 1 in 250 people – but only 1 in 6 of these are diagnosed. Identification of FH is primarily done by clinical diagnosis with subsequent confirmation by genetic testing where possible. Beyond conventional screening methods such as PCR amplification and Sanger sequencing, NGS has shown significant potential with its ability to undertake parallel sequencing relatively quickly.⁶⁸ By systematically using both genetic and biochemical testing, FH can be identified, and affected people can receive inexpensive medicines to protect them from future problems.⁶⁹ Studies have shown that detection and treatment of

63 ABPI (2014). Stratified medicine in the NHS: An assessment of the current landscape and implementation challenges for non-cancer applications. Available at: http://www.abpi.org.uk/our-work/library/medical-disease/Documents/stratified_med_nhs.pdf

64 Pezalla, E. J. (2016). Payer view of personalised medicine. *Am J Health System Pharm.* 73(23).

65 Jakka, S. and Rossbach, M. (2013). An economic perspective on personalised medicine. *The HUGO Journal*, 7(1): 1

66 Personalised Medicine Coalition. The Case for Personalised Medicine. 2014.

67 Licastro, F. and Caruso, C. (2010). Predictive diagnostics and personalised medicine for the prevention of chronic degenerative diseases. *Immunity and Ageing*, 7(1): S1

68 Faiz, F., Allcock, R. et al. Detection of variations and identifying genomic breakpoints for large deletions in the LDLR by Ion Torrent semiconductor sequencing. *Atherosclerosis*. 2013;230(2):249–55.

69 NHS England (2016). Improving outcomes through personalised medicine. Available at: <https://www.england.nhs.uk/wp-content/uploads/2016/09/improving-outcomes-personalised-medicine.pdf>

FH leads to significant savings in healthcare costs.⁷⁰ In the UK, it is estimated that the identification and optimal treatment of all FH cases would save the NHS £380 million over a 55-year period, or £6.9 million per year.⁷¹ When extrapolated to the EU, the savings would yield about €86 million per year.⁷²

Innovation in genetic testing has improved the identification of patients at risk of breast cancer and ovarian cancer. Germline mutations in the BRCA1 and BRCA2 genes are known to be associated with a higher risk of breast and ovarian cancer. Because of the perceived high costs associated with genetic analyses, BRCA1/2 testing has traditionally been restricted to breast cancer patients having a high risk of being a carrier. However, this has started to change following demonstrated benefits. A cost-effectiveness model developed in the UK has shown that BRCA testing of all women with epithelial ovarian cancer each year is cost-effective at a UK willingness-to-pay threshold of £20,000/quality-adjusted life-year (QALY) compared with no testing, with an incremental cost-effectiveness ratio of £4,339/QALY.⁷³

2.2.2. Improving management of diseases

There are also studies showing improvement in management of certain cancers. One example is NSCLC. Patients with advanced NSCLC who can no longer work do not pay into social contribution schemes like health insurance funds, pension funds, or nursing care funds. The productivity losses double when an employed family member becomes a carer for the patient with lung cancer. Additionally, patients who are no longer able to look after themselves will require formal care. Historically, patients with metastatic NSCLC received cytotoxic chemotherapy regimens; however, the discovery of genetic alterations that drive tumour progression in subsets of NSCLC has transformed the clinical management of this disease.⁷⁴

Today, new treatments have extended the time before symptoms worsen, delaying the negative physical and emotional consequences associated with disease progression. Recent developments include the ability to target the PD-1/PD-L1 pathway through the synthesis of monoclonal antibodies (mAbs).⁷⁵

Use of these immunotherapies in combination is starting to be launched across oncology indications. Initially, nivolumab was authorised for market entry as a monotherapy by EMA in 2015, followed by combination with ipilimumab in 2016. Advanced melanoma patients who were given nivolumab plus ipilimumab lived for another 11.5 months without

70 Marks, D., Wonderling, D. et al. Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. *BMJ*. 2002; 324(7349):1303.

71 Heart UK. Saving lives, saving families the health, social and economic advantages of detecting and treating familial hypercholesterolaemia (FH). 2012. Available at: www.heartuk.org.uk/files/uploads/documents/HUK_SavingLivesSavingFamilies_FHreport_Feb2012.pdf. Accessed 15 Jul 2015

72 Wiegman, A., Gidding, S. S. et al. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J*. 2015;36(36):2425–37.

73 Eccleston, A., Bentley, A., Dyer, M., Strydom, A., Vereecken, W., George, A. and Rahman, N. (2017). A cost-effectiveness evaluation of germline BRCA1 and BRCA2 testing in UK women with ovarian cancer. *Value in Health*, 20(4): 567-576.

74 Griffin, R. and Ramirez, R. A. (2017). Molecular Targets in Non-Small Cell Lung Cancer. *Ochsner J*. 2017 Winter;17(4):388-392. <https://www.ncbi.nlm.nih.gov/pubmed/29230123>

75 Yoshiko Iwai, Junzo Hamanishi, Kenji Chamoto and Tasuku Honjo, Cancer immunotherapies targeting the PD-1 signaling pathway, *Journal of Biomedical Science* 2017

their disease getting worse, and patients given only nivolumab lived for another 6.9 months.⁷⁶ Both PM methods delayed disease progression as well as prolonged survival over standard-of-care. However in the future combination-based therapies are likely to replace the current administration and deliver better patient outcomes.

As a results of these developments, molecular classification has entered routine clinical practice, mainly through the identification of molecular therapeutic targets. The 2015 classification of lung cancer now mandates immuno-histochemical and molecular analysis in routine clinical practice.⁷⁷ Treatment algorithms for NSCLC have changed dramatically over the last few years, following the approval of the first generation of targeted therapies (epidermal growth factor receptor (EGFR) inhibitors) for NSCLC, beginning with evidence showing their efficacy in second-line therapy in 2005.⁷⁸

A study conducted in 2012 investigated the savings accrued using a targeted therapy (bevacizumab-based treatment)⁷⁹ for NSCLC from the societal perspective⁸⁰, taking only public costs into account, in France, Germany, Italy, and Spain. As illustrated in Figure 4, this analysis shows that personalised treatment in lung cancer is associated with more savings to society compared to standard chemotherapy in terms of increased productivity and decreased social benefits paid to patients in France, Germany, Italy, and Spain who are able to work. Mean incremental savings to society per patient ranged from €2,277 in Italy to €4,461 in Germany.⁸¹ The results were most sensitive to the change in proportion of patients working full-time and the proportion of patients who were able to return to work.

76 European Medicines Agency (2017) EPAR summary for the public Opdivo (nivolumab). EMA/691693/2017 EMEA/H/C/003985 -

77 Pirker, R. and Filipits, M. (2016). Personalized treatment of advanced non-small-cell lung cancer in routine clinical practice. *Cancer Metastasis Reviews*, 35, 141–150. <http://doi.org/10.1007/s10555-016-9612-6>

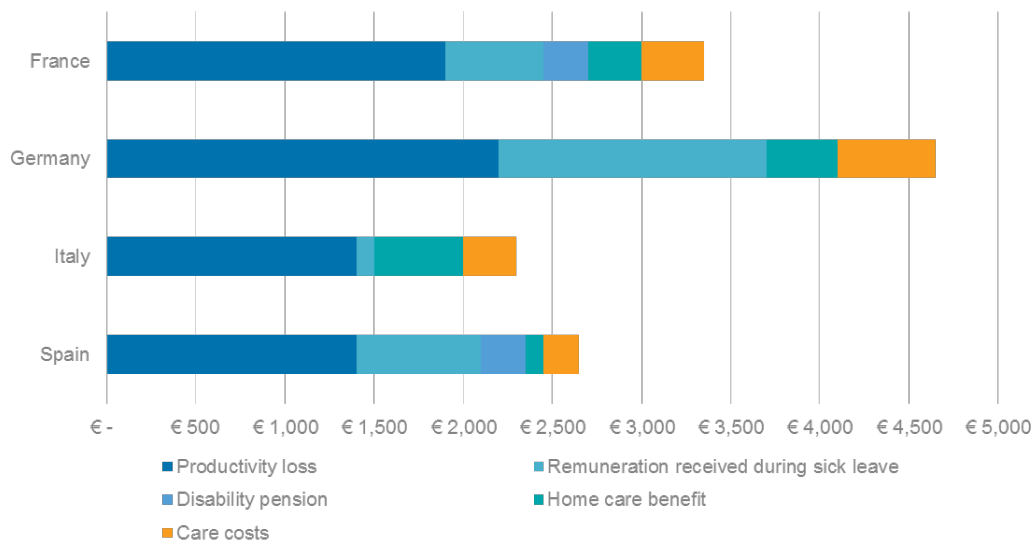
78 Lazzari, C. et al. (2017). Historical evolution of second-line therapy in non-small cell lung cancer. *Front Med (Lausanne)* 4. <https://dx.doi.org/10.3389%2Ffmed.2017.00004>

79 There is debate on whether bevacizumab should be considered an example of PM, as although it is a targeted therapy, a predictive biomarker does not exist for this treatment

80 Societal costs were estimated by collecting and analysing labour costs, carer costs, sickness benefits, disability benefits, and home care benefits. Cost inputs were derived from publicly available databases or from the published literature.

81 Lister, J., Stanistic, S., Kaier, K., Hagist, C., Gulyaev, D. and Walzer, S. (2012). Societal savings in patients with advanced non-squamous non-small-cell lung cancer receiving bevacizumab-based versus non-bevacizumab-based treatments in France, Germany, Italy, and Spain. *ClinicoEconomics and outcomes research: CEOR*, 4,299.

Figure 4: Treatment savings per patient by using bevacizumab plus chemotherapy treatment, relative to only chemotherapy (5-year cumulative savings).



Source: Lister et al. (2012)

2.2.3. Preventing or delaying more expensive care costs and allowing scarce healthcare resources to be used most efficiently

PM can also allow scarce healthcare resources to be used most efficiently. For example, personalised care can decrease the length of hospitalisation. Ultimately, providing PM to patients could improve clinical outcomes and allow healthcare professionals to better allocate hospital resources.⁸²

Reducing use of ineffective therapies for patients

PM can create efficiencies in the healthcare system by reducing the use of therapies for patients for whom the treatment is not effective. Use of genetic testing can also prevent development of diseases or complications.⁸³

Genetic testing can reduce healthcare costs by targeting appropriate early interventions and by optimising the use of chemotherapy. A series of papers have examined the cost-effectiveness of BRCA testing in breast cancer.⁸⁴ Indeed, NICE has also concluded that BRCA testing is cost-effective and that there should be direct referral to a specialist when a high-risk mutation has been identified.

Gene profiling can reduce cost through the effective allocation of patients to chemotherapy or non-chemotherapy treatment regimens, particularly in the early and

82 Katz, G. et al. (2015). Economic impact of gene expression profiling of early stage breast cancer patients in France. *PLoS One*. <https://doi.org/10.1371/journal.pone.0128880>

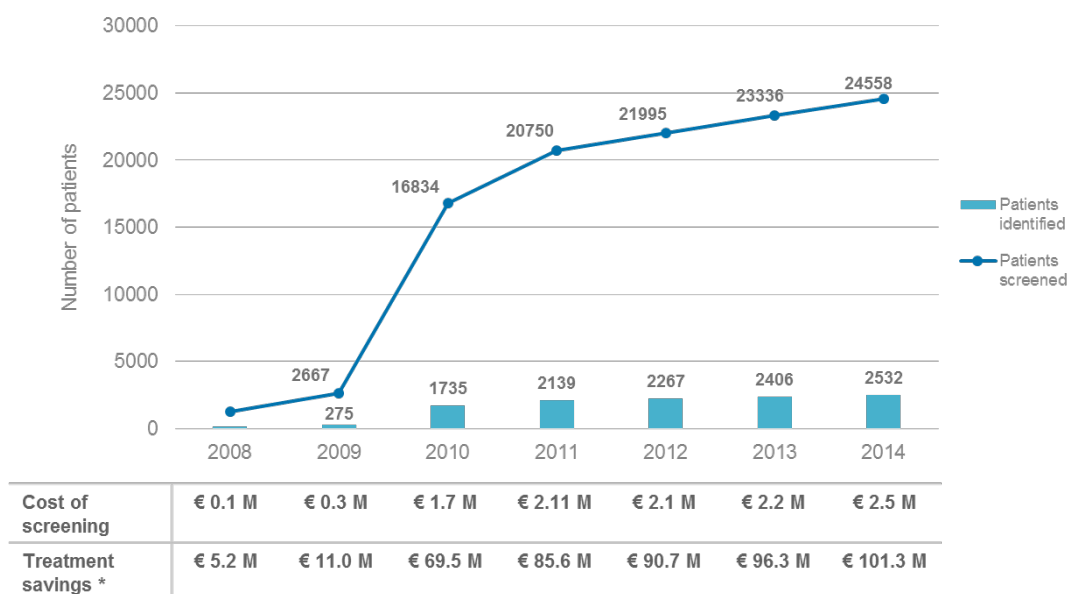
83 PhRMA (2015). Value of personalised medicine. Available at: http://phrma-docs.phrma.org/sites/default/files/pdf/chart_pack-value_of_personalised_medicine.pdf

84 "Cost-effectiveness evidence review - Familial breast cancer: Classification and care of women at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer." Update of clinical guideline 14 and 41

adjuvant setting. A recent French study found that use of gene expression profiling with Oncotype Dx⁸⁵ to inform chemotherapy decision-making meant average costs were €602 lower for patients undergoing testing, due to a reduction in lost productivity.⁸⁶ Expressing cost-effectiveness as an incremental cost-effectiveness ratio (ICER) of incremental costs divided by incremental effectiveness (QALYs) showed that Oncotype DX is likely to be considered highly cost-effective from a healthcare payer perspective, with an ICER of approximately €2,134 per QALY gained versus standard care.

The benefits of this can clearly be seen in lung cancer. In Europe, it is estimated that lung cancer-related premature mortality cost an estimated €17 billion.⁸⁷ In France, following EMA approval of gefitinib in June 2009 for EGFR-positive NSCLC, the French National Cancer Institute (INCa) allocated an additional €1.7 million to regional genetics centres across the country for EGFR testing. As illustrated in Figure 5, this resulted in a substantial increase in screening. INCa deduced that the additional investment would save the French health insurance industry €69 million by ensuring that gefitinib would be prescribed only to those patients who had been identified as harbouring the EGFR mutation and thus were more likely to respond to treatment.⁸⁸

Figure 5: Number of lung cancer patients screened for EGFR mutations, cost of screening and associated treatment savings resulting from targeted treatment



85 Oncotype DX is a validated gene expression profiling test that predicts the likelihood of adjuvant chemotherapy benefit in early stage breast cancer. The cost-effectiveness of using the Oncotype DX Recurrence Score (RS) to guide chemotherapy decision-making was compared with standard care.

86 Katz, G. et al. (2015). Economic impact of gene expression profiling in patients with early stage breast cancer in France. *PLoS One*, 18. <https://doi.org/10.1371/journal.pone.0128880>

87 Davies, J., Patel, M., Gridelli, C., de Marinis, F., Waterkamp, D. and McCusker, M. E. (2017). Real-world treatment patterns for patients receiving second-line and third-line treatment for advanced non-small cell lung cancer: A systematic review of recently published studies. *PLoS ONE*, 12(4): e0175679. <http://doi.org/10.1371/journal.pone.0175679>

88 Nowak, F. (2012). Personalised medicine: A nationwide initiative for an equal access to cancer treatment in France. Presentation at *EuroBioForum 2012*

Source: WIN Consortium

According to the Spanish Society of Medical Oncology (SEOM) and the Spanish Society of Pathology (SEAP), diagnostic and treatment recommendations for advanced NSCLC patients based on molecular testing provides an opportunity to improve healthcare efficiency and resource use.⁸⁹ We can also draw lessons from the United States to obtain more quantitative economic evidence. It is estimated that \$604 million in annual healthcare cost savings would be realised if patients with metastatic colorectal cancer received a genetic test for the KRAS gene prior to treatment.⁹⁰ Indeed, studies in both the US and Europe indicate that a 34% reduction in chemotherapy use would occur if women with breast cancer receive a genetic test of their tumour prior to treatment.^{91,92}

Reducing hospital stays

The development of PM has an impact on the costs of cancer treatment in health facilities, through a decrease in hospital stays and the progress of consultations.

- In the Netherlands, oncologists report that across oncology as a whole, PM has reduced chemotherapy usage and hospital stays, despite the additional product acquisition cost of targeted treatments.⁹³ It is estimated that the mean hospital stay for targeted treatments is 3–4 days, whereas previously it was more than a week for chemotherapy regimens.⁹⁴
- In France, 293,628 people were hospitalised with chemotherapy in 2013. However, as the use of PM therapies has increased, the overall number of hospital stays (public and private) has decreased by 2.7% (260,390 stays in 2012 and 253,392 in 2013).
- In 2013, NHS England sanctioned a faster method of administering a targeted breast cancer product, trastuzumab, to breast cancer patients. They noted that as well as being less invasive for the patient, the new formulation saves time for nurses and hospital pharmacies in both its preparation and administration. This will free up specialist cancer nurses and hospital pharmacists at a time when pressure on chemotherapy facilities continues to rise.⁹⁵ A study of the socio-economic impact of intravenous (IV) versus subcutaneous (SC) administration

89 Garrido, P., de Castro, J., Concha, Á., Felip, E., Isla, D., López-Ríos, F., ... and Gómez, J. J. (2012). Guidelines for biomarker testing in advanced non-small-cell lung cancer. A national consensus of the Spanish Society of Medical Oncology (SEOM) and the Spanish Society of Pathology (SEAP). *Clinical and Translational Oncology*, 14(5): 338-349.

90 Akhmetov, I. and Bubnov, R. V. (2015). Assessing value of innovative molecular diagnostic tests in the concept of predictive, preventive, and personalized medicine. *EPMA Journal*, 6, 19. <http://doi.org/10.1186/s13167-015-0041-3>

91 Genomic Health. Health Economics. Genomic Health web site. (Available at: <http://www.genomichealth.com/en-US/Publications/HealthEconomics.aspx#U446Q5SwK0I>)

92 Albanell, J., Svedman, C., Gligorov, J., Holt, S. D., Bertelli, G., Blohmer, J. U., ... & Eiermann, W. (2016). Pooled analysis of prospective European studies assessing the impact of using the 21-gene Recurrence Score assay on clinical decision making in women with oestrogen receptor–positive, human epidermal growth factor receptor 2–negative early-stage breast cancer. *European Journal of Cancer*, 66, 104-113.

93 Dutch medical oncologist interview

94 Ibid

95 NHS England News, 24 September 2013. "NHS England sanctions new breast cancer treatment injection".

suggested that this change in administration could result in a cost saving of an estimated €19.2 million for the NHS.⁹⁶

2.2.4. Summary

The evidence showing the benefits of PM on healthcare systems and society is summarised below.

Table 8: The impact of personalised medicine on healthcare systems and society

Type of impact	Key findings
Focus on prevention and prediction of disease	<ul style="list-style-type: none"> • Familial hypercholesterolemia (FH) causes a significant risk of heart attack in the under 50s. Early identification through genetic testing and treatment of FH has led to significant savings in healthcare costs (e.g. estimated at £380 million over a 55-year period in the UK, or £6.9 million/year).⁹⁷ • The demonstrated benefits of testing for germline mutations in BRCA1/2, which are associated with higher risks of breast and ovarian cancer, has led to the incorporation of this testing in national guidelines (e.g. INCa in France). • A cost-effectiveness model in England has shown that BRCA testing of all women with epithelial ovarian cancer each year is cost-effective at a UK willingness-to-pay threshold of £20,000/quality-adjusted life-year (QALY) compared with no testing.⁹⁸
Improvement in patient management	<ul style="list-style-type: none"> • Historically, patients with metastatic NSCLC received cytotoxic chemotherapy regimens; however, the discovery of EGFR and anaplastic lymphoma kinase (ALK) rearrangements (mutations) has transformed the clinical management of this disease and led to better patient outcomes.^{99 100} • A study investigating the societal savings accrued using targeted therapy in NSCLC across EU markets illustrated the mean incremental savings to society per patient ranged from

⁹⁶ Papadmitriou, K., Trinh, X. B., Altintas, S., Van Dam, P. A., Huizing, M. T. and Tjalma, W. A. A. (2015). The socio-economical impact of intravenous (IV) versus subcutaneous (SC) administration of trastuzumab: future prospectives. *Facts, Views and Vision in ObGyn*, 7(3): 176–180.

⁹⁷ Marks D, Wonderling D, et al. Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. *BMJ*. 2002; 324(7349):1303.

⁹⁸ Eccleston, A., Bentley, A., Dyer, M., Strydom, A., Vereecken, W., George, A. and Rahman, N. (2017). A cost-effectiveness evaluation of germline BRCA1 and BRCA2 testing in UK women with ovarian cancer. *Value in Health*, 20(4): 567-576.

⁹⁹ Griffin, R. and Ramirez R.A. (2017). Molecular Targets in Non-Small Cell Lung Cancer. *Ochsner J*. 2017 Winter;17(4):388-392. <https://www.ncbi.nlm.nih.gov/pubmed/29230123>

¹⁰⁰ Drezet, A., Loubière, S., Wislez, M., Beau-Faller, M., Nanni-Métellus, I., Garcia, S., ... and Duruisseaux, M. (2016). Cost-effectiveness of KRAS, EGFR and ALK testing for therapeutic decision making of advanced stage non-small cell lung cancer (NSCLC): the French IFCT-PREDICT. amm study. *Annals of Oncology*, 27(suppl_6).

	€2,277 in Italy to €4,461 in Germany, primarily by reducing productivity loss and remuneration received during sick leave. ¹⁰¹
Reduction in use of ineffective therapies for patients	<ul style="list-style-type: none"> • Studies in the US and Europe indicate that there could be a 34% reduction in chemotherapy use if women with breast cancer received a genetic test of their tumour prior to treatment.^{102,103} • A study of the economic impact of the Oncotype DX Test in patients with early stage breast cancer (a gene expression profiling test that predicts the likelihood of adjuvant chemotherapy benefit) found that costs were on average €602 lower for patients whose treatment was modified as a result of the testing, compared to patients receiving standard care. The savings were due to fewer days off work associated with chemotherapy and management of side effects.¹⁰⁴ • In France, INCa deduced that an additional €1.7 million investment in regional genetics centres for EGFR testing would save the French health insurance industry €69 million by identifying patients who harboured the EGFR mutation and thus ensuring the treatment was only prescribed to patients who were more likely to respond.¹⁰⁵
Reduction in hospital stay	<ul style="list-style-type: none"> • In the Netherlands, oncologists estimate that the mean hospital stay for targeted treatments is 3–4 days, whereas previously it was more than a week for chemotherapy regimens.¹⁰⁶ • In France, 293,628 people were hospitalised with chemotherapy in 2013. However, the increasing use of PM therapies has decreased the overall number of stays (public

101 Lister, J., Stanistic, S., Kaier, K., Hagist, C., Gulyaev, D. and Walzer, S. (2012). Societal savings in patients with advanced non-squamous non-small-cell lung cancer receiving bevacizumab-based versus non-bevacizumab-based treatments in France, Germany, Italy, and Spain. *ClinicoEconomics and outcomes research*: CEOR, 4, 299.

102 Genomic Health. Health Economics. Genomic Health web site. (Available at: <http://www.genomichealth.com/en-US/Publications/HealthEconomics.aspx#.U446Q5SwK0I>).

103 Albanell, J., Svedman, C., Gligorov, J., Holt, S. D., Bertelli, G., Blohmer, J. U., ... & Eiermann, W. (2016). Pooled analysis of prospective European studies assessing the impact of using the 21-gene Recurrence Score assay on clinical decision making in women with oestrogen receptor–positive, human epidermal growth factor receptor 2–negative early-stage breast cancer. *European Journal of Cancer*, 66, 104–113.

104 Akhmetov, I. and Bubnov, R. V. (2015). Assessing value of innovative molecular diagnostic tests in the concept of predictive, preventive, and personalized medicine. *EPMA Journal*, 6, 19. <http://doi.org/10.1186/s13167-015-0041-3>

105 Nowak, F. (2012). Personalised medicine: A nationwide initiative for an equal access to cancer treatment in France. Presentation at *EuroBioForum 2012*

106 Dutch medical oncologist interview

and private) by 2.7% (260,390 stays in 2012 and 253,392 in 2013).¹⁰⁷

- In 2013, NHS England sanctioned a faster method of administering trastuzumab for targeted breast cancer treatment. They noted that as well as being less invasive for the patient, the new formulation saves time for nurses and hospital pharmacies in both its preparation and administration, with a potential cost saving of €19.2 million for the NHS.¹⁰⁸

Source: CRA analysis

2.3. More efficient development of novel medicines

As understanding of the molecular nature of diseases increases, disease classifications are likely to become even more precise and be extended into more diverse cancer types. Developments in PM will directly impact the design and recruitment of clinical trials and could therefore induce a fundamental change in medicine development.¹⁰⁹ Further, development in genomic technologies, such as WES, provides the opportunity to detect recurrent alterations in genes not previously implicated in cancer, and is therefore useful for initial basic research and discovery of molecular targets.¹¹⁰

2.3.1. More effective clinical trials

Biomarkers have been used within clinical trials to facilitate drug development for different purposes, such as to serve as indicators of a medicine's toxicity or efficacy or to identify specific patient populations for targeted treatments.¹¹¹ The proportion of trials using pharmacogenetics or pharmacogenomic (PGX) biomarkers to target specific patients continually increased (see Figure 6).

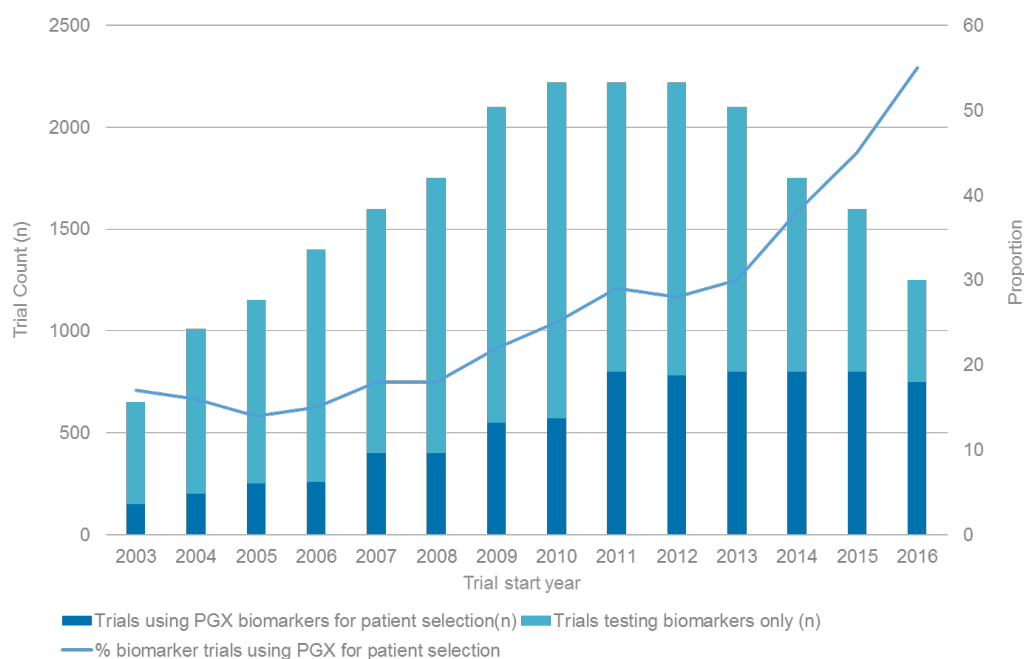
107 Katz, G. et al. (2015). Economic impact of gene expression profiling of early stage breast cancer patients in France. *PLoS One*. <https://doi.org/10.1371/journal.pone.0128880>

108 Papadimitriou, K., Trinh, X. B., Altintas, S., Van Dam, P. A., Huizing, M. T. and Tjalma, W. A. A. (2015). The socio-economical impact of intravenous (IV) versus subcutaneous (SC) administration of trastuzumab: future perspectives. *Facts, Views and Vision in ObGyn*, 7(3): 176–180.

109 Jakka, S. and Rossbach, M. (2013). An economic perspective on personalised medicine. *The HUGO Journal*, 7(1): 1

110 Dong, L., Wang, W., Li, A., Kansal, R., Chen, Y., Chen, H. and Li, X. (2015). Clinical Next Generation Sequencing for Precision Medicine in Cancer. *Current Genomics*, 16(4): 253–263. <http://doi.org/10.2174/1389202915666150511205313>

111 Pharma Intelligence (2017). One Size No Longer Fits All: The Personalised Medicine Trial Landscape.

Figure 6: Phase I-IV clinical trials utilising biomarkers by trial start year, 2003–2016

Source: *Pharma Intelligence*

Studies have shown that when PM approaches are used as a selection strategy in clinical trials, this can lead to more effective results:

- A meta-analysis comparing patient outcomes in phase I clinical studies that used a biomarker-based (personalised) cancer treatment strategy found that this approach was associated with significantly improved outcomes (response rate (RR) and progression-free survival (PFS)).¹¹²
- Increased use of biomarkers as inclusion or exclusion criteria has led to improvements in probability of success across all four phases of development.¹¹³ The benefit from using biomarkers raises the likelihood of approval from phase I to one in four, compared to less than one in 10 when no selection biomarker was used (see Figure 7).

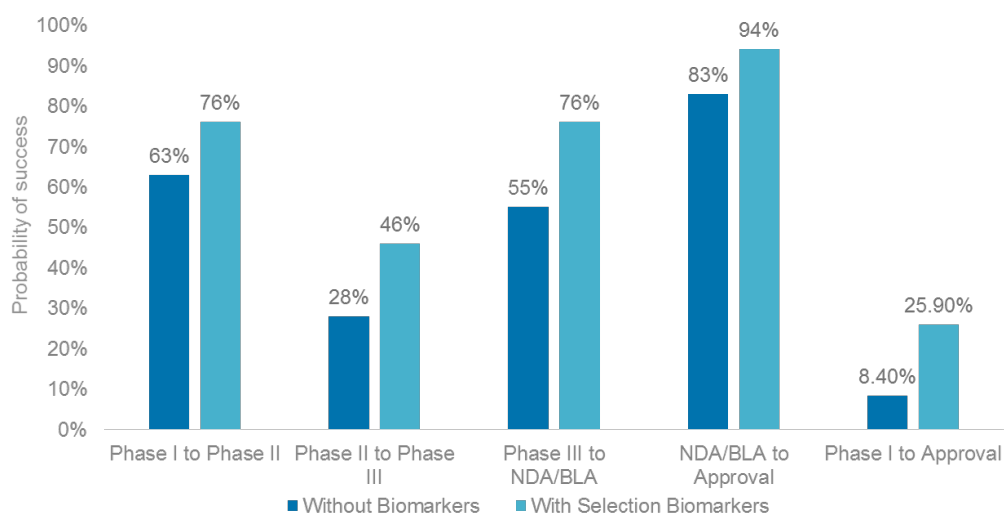
This better understanding of genetic variations helps scientists identify new disease sub-groups and their associated molecular pathways, allowing research into targeted therapies.¹¹⁴ Molecular analysis could also help select patients for inclusion, or exclusion, in late-stage clinical trials, helping to gain approval for medicines that might otherwise be abandoned because they appear to be ineffective in a large cohort of patients.¹¹⁵

112 Schwaederle M, Zhao M, Lee JJ, et al. Association of Biomarker-Based Treatment Strategies With Response Rates and Progression-Free Survival in Refractory Malignant Neoplasms: A Meta-analysis. *JAMA Oncol.* 2016;2(11):1452-1459

113 BIO (2016). Clinical Development Success Rates 2006-2015

114 Barh, D., Dhawan, D. and Ganguly, N. K. (Eds.). (2013). *Omics for personalised medicine*. Springer.

115 Hong, K. W. and Oh, B. S. (2010). Overview of personalised medicine in the disease genomic era. *BMB reports*, 43(10): 643-648.

Figure 7: Probability of success with and without selection biomarkers

Source: BIO

2.3.2. More efficient clinical trials and reduction of R&D costs

PM has resulted in changing clinical trial methodology, which now focuses on individual, rather than average, responses to therapy.¹¹⁶ Researchers can now consider genetic and other environmental factors that shape a person's response to a particular treatment, and they can adapt trials in order to better account for variability between patients. The aim is to be able to divide patients into genetic subgroups that influence their responses to treatments. This results in smaller, more streamlined trials, which can also reduce development costs and high rates of failure.^{117,118}

2.3.3. More ethical trials

There is also an ethical dimension. There may be situations in which conducting a large randomised phase III clinical trial to gain regulatory approval is impractical or even unnecessary.¹¹⁹ It has been argued that in an era of PM, molecularly validated targeted agents have demonstrated convincing efficacy in early stage clinical testing.¹²⁰ Small trials expose only a minimum number of patients to the controversial risks and burdens of trial participation. There is therefore a strong ethical rationale in having trials that involve the least number of patients necessary to achieve a conclusion, and potentially supplementing this with real world evidence once the product is authorised.¹²¹

116 Schork, N. J. (2015). Personalized medicine: time for one-person trials. *Nature*, 520(7549): 609-611.

117 Deverka, P. A., Vernon, J. and McLeod, H. L. (2010). Economic opportunities and challenges for pharmacogenomics. *Annual review of pharmacology and toxicology*, 50, 423-437.

118 OECD (2011) Policy issues for the development and use of biomarkers in health.

119 Selaru, P., Tang, Y., Huang, B., Polli, A., Wilner, K. D., Donnelly, E. and Cohen, D. P. (2016). Sufficiency of Single-Arm Studies to Support Registration of Targeted Agents in Molecularly Selected Patients with Cancer: Lessons from the Clinical Development of Crizotinib. *Clinical and translational science*, 9(2): 63-73.

120 Sharma, M. R. and Schilsky, R. L. (2012). Role of randomized phase III trials in an era of effective targeted therapies. *Nature reviews Clinical oncology*, 9(4): 208-214.

121 Vaidyanathan, G. (2012). Redefining clinical trials: the age of personalized medicine. *Cell*, 148(6): 1079-1080.

2.3.4. Summary

The evidence of PM providing more efficient development of novel medicines is summarised below.

Table 9: The impact of personalised medicine on clinical research and development

Type of impact	Key findings
More effective clinical trials	<ul style="list-style-type: none"> Increased use of biomarkers for patient selection in phase I–IV clinical trials, from 20% in 2003, rising to 57% in 2016, leads to more effective clinical trials.¹²² Personalised cancer treatments have response rates that are significantly higher with genomic vs protein biomarkers, indicating the effectiveness of a more targeted approach.¹²³ Using selection biomarkers raises the probability of success from phase I to approval from 8.5% to 25.9%.¹²⁴
More efficient clinical trials	<ul style="list-style-type: none"> Subdivision of patients into genetic groups that dictate their responses to treatments results in smaller, more streamlined trials, which can also reduce the immense development costs and high rates of failure.¹²⁵
More ethical trials	<ul style="list-style-type: none"> Small trials expose only a minimum number of patients to the controversial risks and burdens of trial participation. There is a strong ethical rationale in having trials involve the smallest number of patients necessary to achieve a conclusion, and potentially supplementing this with real world evidence once the product is authorised.¹²⁶

Source: CRA analysis

2.4. Conclusion

Following data reviewed in Chapter 2, there is considerable evidence showing that PM brings benefits for patients, clinicians, healthcare systems and the wider clinical development process in Europe. However, empirical evidence is clearly stronger in the US than in Europe.

To date, few studies have compared access to PM in different European markets. We examine this in the next chapter.

¹²² Pharma Intelligence (2017). One Size No Longer Fits All: The Personalised Medicine Trial Landscape.
¹²³ Schwaederle M, Zhao M, Lee JJ, et al. Association of Biomarker-Based Treatment Strategies With Response Rates and Progression-Free Survival in Refractory Malignant Neoplasms: A Meta-analysis. *JAMA Oncol.* 2016;2(11):1452-1459
¹²⁴ BIO (2016). Clinical Development Success Rates 2006-2015
¹²⁵ OECD (2011) Policy issues for the development and use of biomarkers in health.
¹²⁶ Vaidyanathan, G. (2012). Redefining clinical trials: the age of personalized medicine. *Cell*, 148(6): 1079-1080.









3. The environment for personalised medicine

This chapter considers the environment for PM, focusing particularly on our therapeutic case studies (breast, lung, ovarian and skin cancers) and the experience in five European countries (Denmark, England, France, the Netherlands, Poland). Other notable country examples from the literature are also included. The aim is to establish the barriers to the use of PM and the enablers, as well as to identify some key aspects of how this may evolve in the future (particularly as innovative technologies such as cell and gene therapies are launched in Europe and genomic technologies evolve). We draw on both secondary research and the insights provided in the external interviews.

3.1. Recognition of personalised medicine as a policy priority

The first issue identified in the interviews as important for the use and development of PM was whether PM has been identified as a policy priority by a member state's government (with an established stand-alone national plan) or whether personalisation was considered in national cancer plans.¹²⁷ As illustrated in Table 10, there are a mix of approaches to prioritising PM in terms of healthcare policy across EU markets.

Table 10: Policy prioritisation for select EU markets

Country	Policy prioritisation	Description
Denmark		<ul style="list-style-type: none"> Key focus within National Cancer Plans Recent National Strategy for PM (2017–2020)
England		<ul style="list-style-type: none"> PM strategy through NHS England Focus of increased integration of genomics and diagnostics into the NHS
Estonia		<ul style="list-style-type: none"> PM program (2016–2020) managed by the Ministry of Social Affairs
France		<ul style="list-style-type: none"> Key focus within National Cancer Plans PM strategy on 'Genomic Medicine 2025'
Germany		<ul style="list-style-type: none"> National plan on PM that focuses on new priorities for government funding
Italy		<ul style="list-style-type: none"> PM included within agenda for sustainable healthcare
The Netherlands		<ul style="list-style-type: none"> Government acknowledges PM in Medicines Plan and it is included in research agenda for sustainable health
Poland		<ul style="list-style-type: none"> No specific plan on PM Access to diagnostics included as an objective in the National Cancer Plan

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The European Commission has also encouraged countries to develop national cancer control plans.

Notes: Green – High (dedicated national plan on PM); Amber – Medium (inclusion of PM in health strategies or national cancer plans); Red – Low (no policies on PM)

Source: CRA analysis

The clear benefit of having a PM strategy in addition to a national cancer plan (NCP) is that it allows a forward-looking perspective on the value of genomics to the healthcare system; it supports the testing infrastructure towards the development of WGS, which is also applicable to other conditions outside oncology, such as rare diseases. This leads to infrastructure changes and associated benefits to be gained across the whole healthcare system. Therefore, the overall objective of the PM plans in these countries is to focus on (1) investing in infrastructure in order to improve diagnostic capacity; and (2) the strategy in terms of a centralising process. As set out in Table 11, countries have adopted different approaches to implementation; however, they contain some common elements:

Table 11: Implementation of PM strategies in selected countries

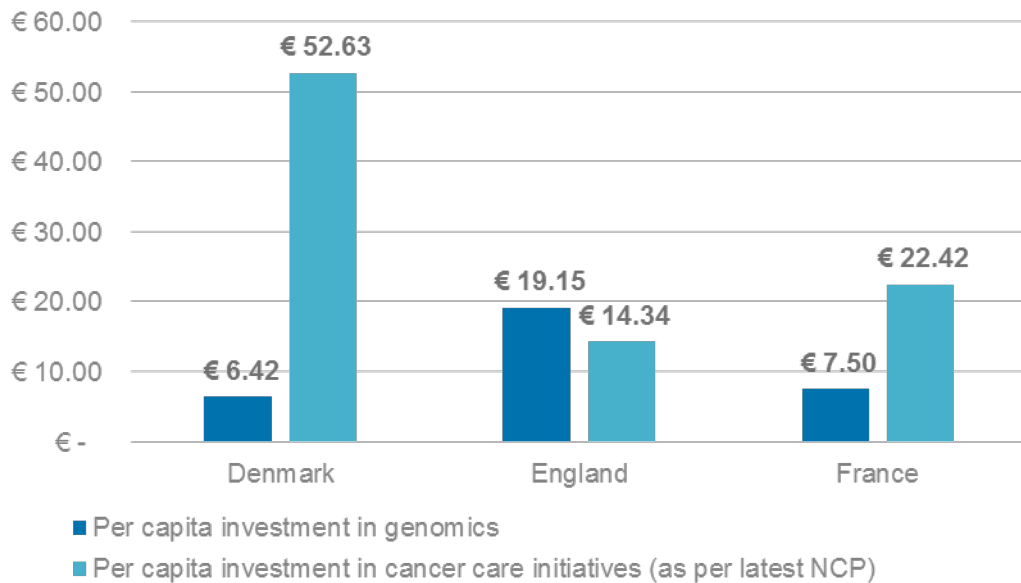
Denmark	Denmark began implementing NCPs earlier than other European countries; the first plan was published in 2000. ¹²⁸ In 2017 Denmark opened a national genome centre for PM, which will serve as a hub for integrating genomic data, incorporating current information sources such as biobanks and national registries. ¹²⁹
Estonia	Estonia proposed an ambitious PM program in June 2000. As of February 2014, the Estonian Genome Project Foundation had collected data from 52,000 adult donors. ¹³⁰
France	France initially invested centrally in molecular diagnostics and infrastructure as part of its NCP, with the development the French National Cancer Institute (INCa) in 2004. In 2016, France announced the ‘France Médecine Génomique 2025’ program, aiming to open 12 sequencing centres and ensure 235,000 WGS a year. The French government is planning to inject €670M in this program. ¹³¹
Ireland	Genomics Medicine Ireland (GMI) has raised €36m (\$40m) to sequence the genome of the Irish population and use the information to develop new drugs and diagnostics. ¹³²
England	England has relied on a decentralised model allowing lots of variation in funding and usage, but was the first in Europe to launch a program dedicated to WGS. Genomics England aims to sequence up to 100,000 whole genomes from patients through 13 Genomic Medicine Centres. ¹³³ NHS England is supporting the integration of genomics into its services

128 Ministry of Health and Danish Regions. Summary of National Strategy for Personalised Medicine 2017-2020
 129 Healthcare Denmark, 1 March 2017. “New Danish genome centre for research on personalised medicine.”
<http://healthcaredenmark.dk/news/new-danish-genome-centre-for-research-on-personalized-medicine.aspx>
 130 Ibid
 131 Cynober, T. (2017) The Past, Present and Future of Genome Sequencing – labiotech.eu;
 132 Rodríguez Fernández, C. (2016) €36M Fundraising to Sequence the Genome of Ireland – labiotech.eu;
 133 NHS England (2016). Improving outcomes through personalised medicine

through setting up a new national network of Genomic Laboratory Hubs (GLHs) by November 2018. ¹³⁴
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Countries have clearly taken account of the advances in genomic technologies and their application in clinical practise by making substantial investments in this space. In England, Denmark and France, per capita investments in genomics and increasing diagnostic capacity is a clear priority (see Figure 8).

Figure 8: Per capita investment in genomics compared to other cancer initiatives



Source: CRA analysis of various sources¹³⁵

There is clearly a question about what to focus on: supporting diagnostics testing, profiling, or WGS. Most countries in Europe have prioritised WGS rather than increasing uptake of NGS technology for more genomic profiling of tumours within current clinical pathways.¹³⁶ Indeed, the different sequencing approaches, as explained in Section 1.1, represent trade-offs in terms of sequencing breadth and depth but also practicality of overall adoption.¹³⁷

Tumour profiling can provide decisive information on the histopathological classification, reveal targets for therapy, indicate drug resistance and give prognostic information. The

¹³⁴ British Journal of Healthcare Computing, 13 October 2017. NHS England network of genomic laboratory hubs to become operational in 2018. Available at: <http://www.bj-hc.co.uk/nhs-england-network-genomic-laboratory-hubs-become-operational-2018>

¹³⁵ Denmark: Genome Web, 17 May 2017. "Denmark to Make Genomic Data Centerpiece of New \$14.2M Personalized Medicine Initiative."; CPH Post Online, 18th November 2017. "Danish government releases 2017 budget." England: CRUK. Achieving world-class cancer outcomes: A strategy for England 2015-2020. France: Genome Web, 23 June 2016. "France plans to Invest €670M in Genomics, Personalized Medicine."; Challenges, 14 February 2014. "Santé : 1,5 milliard d'euros pour le 3e plan cancer."

¹³⁶ Interview with industry

¹³⁷ The Genomic Portrait of Iceland. Hyman, D. M., Taylor, B. S. and Baselga, J. (2017). Implementing genome-driven oncology. *Cell*, 168(4): 584-599.

advantages of this more targeted panel sequencing, in comparison to WES or WGS, include lower costs, easier bioinformatics interpretation, faster sample throughput and lower data storage requirements.¹³⁸ Thus, to ensure that greater numbers of patients are more quickly identified in order to benefit from treatments currently available, clinical genomic profiling strategies should be better optimised to screen more patients, using sufficiently broad targeted gene panels, rather than fewer patients with WGS.¹³⁹

The current health economic evidence base to support the more widespread use of WGS and WES in clinical practice is very limited.¹⁴⁰ There have been many studies examining the cost-effectiveness of NGS technologies to improve patient outcomes; however, it is difficult to make a broad statement about these technologies given that this can depend on clinical context, study timing, patient population, and other health system factors.¹⁴¹ With the cost of WGS decreasing exponentially, in addition to the time it takes to sequence a human genome, the application of WGS as part of routine clinical practice may be more feasible as part of a medium- to long-term policy goal.

Although the PM plans set out the aspiration, no European country at this stage appears to have healthcare policies for PM which place a priority on providing access for novel PM medicinal products specifically. Thus there is no direct correlation between a national plan for PM and access to medicines. Likewise, the absence of a national plan does not mean that patients do not have access to PM. England is an example of a market with active policy in PM and yet with significant access challenges for innovative products.

Looking towards future emerging technologies, cell and gene therapies (which to date target both cancer and rare genetic diseases) will require countries to ensure that treatment centres can meet stringent clinical guidelines for (for example) collection of patient tissue, coordination with a manufacturer-controlled supply chain, and administration of products. Whilst the clinical promise of such cell and gene therapies is high, they are likely to require even more coordination of different elements of the healthcare system, making the value of a national plan even more important.

A coherent PM strategy is a key enabler to the uptake of personalised medicine, encouraging this through increasing coordination of activities across healthcare systems, developing critical infrastructure, and increasing diagnostic capacity. A coherent PM strategy should also articulate the approach to profiling versus WGS.

3.2. Care environment

The second issue identified as important for the use of PM is the care environment. Across countries it is clear that the care environment and the organisation of hospital-based healthcare is constantly changing, reflecting pressure to improve efficiency and help manage budgetary challenges. PM presents additional challenges to healthcare

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- 138 Müllauer, L. (2017). Next generation sequencing: clinical applications in solid tumours. *Magazine of European Medical Oncology*, 10(4): 244-247.
- 139 Hyman, D. M., Taylor, B. S. and Baselga, J. (2017). Implementing genome-driven oncology. *Cell*, 168(4): 584-599.
- 140 Schwarze, K., Buchanan, J., Taylor, J. C. and Wordworth, S. (2018). Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. *Genetics in Medicine*.
- 141 Hatz, M. H., Schremser, K. and Rogowski, W. H. (2014). Is individualized medicine more cost-effective? A systematic review. *Pharmacoeconomics*, 32(5): 443-455.

systems to ensure the availability of diagnostics, and treatments are matched with the availability of clinical expertise to appropriately use such technologies. Trends in the case study markets show how European markets are responding to this challenge:

- **Centralisation by tumour type:** Denmark and the Netherlands
- **'Hub-and-spoke' delivery of oncology care:** England
- **Accredited hospital networks:** France and Poland

Countries centralise cancer care to varying degrees, and in many countries this also varies by therapy area. In the Netherlands, for example, the concentration of care and expertise for melanoma and ovarian cancer patient in specific hospitals allows for better uptake and more effective use of personalised treatments.¹⁴² Indeed, studies have shown that, following centralisation of ovarian cancer treatment in 2012, the Netherlands had better survival rates in 2012–2015 than in 2006–2011.¹⁴³ By comparison, interviewees in the Netherlands report that care for EGFR+ NSCLC is not as centralised, resulting in variation of treatment approach between academic and non-academic centres and lower access to novel PM.¹⁴⁴

Denmark, on the other hand, has greater centralisation of oncology treatment and care, stemming from the introduction of national cancer pathways and the establishment of the Danish Multidisciplinary Cancer Groups (DMCGs).¹⁴⁵ In 2012 a new cancer patient pathway for patients with non-specific symptoms and signs of cancer (NSSC-CPP), increasing the opportunity for targeted therapies, was introduced in Denmark.¹⁴⁶ Standardised cancer package pathways have reduced waiting times, and together with the pooling of medical specialities at fewer units and hospitals, this has also improved the quality of medical care and the quality experienced by patients.¹⁴⁷

In England, expertise has been clustered through a more 'hub-and-spoke' delivery of cancer care. Patients benefit from a cancer management strategy formulated by a multidisciplinary team (MDT) found across cancer units in general hospitals, and specialist MDTs are more likely to be located in larger specialised hospitals.¹⁴⁸ Integrated information and communication technology (ICT) networks support electronic patient records and real-time data sharing, which allows clinicians to collaborate in the delivery of

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- 142 Interview with Dutch pathologist
- 143 Timmermans, M., Schuurman, M. S., Ho, V. K., Massuger, L. F., Nijman, H. W., van Gorp, T., ... and van der Aa, M. A. (2018). Centralization of ovarian cancer in the Netherlands: Hospital of diagnosis no longer determines patients' probability of undergoing surgery. *Gynecologic oncology*, 148(1): 56-61.
- 144 Van der Linden, N. et al. (2017) Treatment Patterns and Differences in Survival of Non-Small Cell Lung Cancer Patients Between Academic and Non-Academic Hospitals in the Netherlands. *Clinical Lung Cancer* 18. <https://doi.org/10.1016/j.clcc.2015.11.011>
- 145 Copenhagen Science City (2015) The Danish model for cancer treatment and prevention- https://nextpartnership.dk/wp-content/uploads/2015/02/ESMO_Folder_WEB.pdf
- 146 Jørgensen, S. F., Ravn, P., Thorsen, S. and Worm, S. W. (2017). Characteristics and outcome in patients with non-specific symptoms and signs of cancer referred to a fast track cancer patient pathway; a retrospective cohort study. *BMC cancer*, 17(1): 809.
- 147 Copenhagen Science City (2015) The Danish model for cancer treatment and prevention- https://nextpartnership.dk/wp-content/uploads/2015/02/ESMO_Folder_WEB.pdf
- 148 Pittathankal, A., and Davidson, T. (nd) "Care pathways for patients with breast cancer". Available at <http://onlinelibrary.wiley.com/doi/10.1002/tre.144/pdf>

effective services between local and more-specialised centres. This means that patients travel to the central hub only when essential for diagnosis and/or treatment.¹⁴⁹

In France, however, accredited hospital networks recognised by INCa coordinate institutions in the region with cancer activities.¹⁵⁰ A similar model is being implemented in Poland, with efforts to improve the care environment to better integrate PM. Patient surveys of the current referral system indicate that the majority of patients were dissatisfied with the length of time taken to diagnose cancer and the lack of communication from healthcare professionals.¹⁵¹ From January 2018, approximately 93% of hospital funding in Poland will be allocated to new hospital networks, organised as linked groups of hospitals with longer-term contracts to deliver patient services for a given area.¹⁵² These networks are intended to improve Poland's capacity to ensure access to PM across the country.¹⁵³

Whilst there is not necessarily a single model or solution, the alignment of expertise and access to innovative medicines is critical to realising the value of PM. Centralisation of care delivery allows concentration of resources and expertise at specialised institutions in order to ensure high quality care delivery and increased efficiency. As illustrated in Figure 9, there is evidence that increasing centralisation and better coordination of care reduced the delay to diagnosis and treatment in lung cancer.

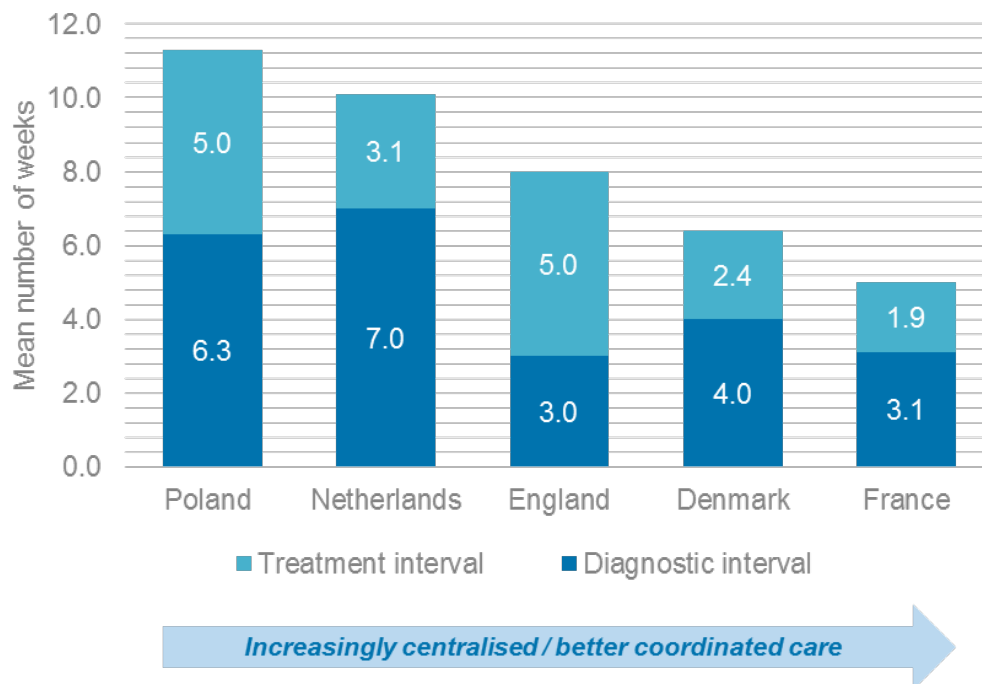
149 Building Better Healthcare, 19 December 2016. "Cancer centres: Designing for wellbeing and improved outcomes".

150 Institut national du Cancer website (2016) L'organisation de l'offre de soins Traitements du cancer : les établissements autorisés Les autorisations de traitement du cancer <http://www.e-cancer.fr/Professionnels-de-sante/L-organisation-de-l-offre-de-soins/Traitements-du-cancer-les-etablissements-autorises/Les-autorisations-de-traitement-du-cancer>

151 Godlewski, D., Adamczak, M. and Wojtyś, P. (2017). Experiences of cancer patients in Poland throughout diagnosis and treatment. *European journal of cancer care*, 26(2).

152 Government Hospital Network Project, <http://siecszpitali.mz.gov.pl/>

153 Polish medical oncologist interview

Figure 9: Weeks from first symptoms to diagnosis (diagnostic interval), and diagnosis to treatment (treatment interval) in lung cancer

Source: CRA analysis of various sources: Poland; Netherlands; England; Denmark; France¹⁵⁴

A key challenge associated with the uptake of PM is the availability of specialised testing services to identify patient specific biomarkers. In order to facilitate access to testing, there many countries have been concentrating expertise in specialised treatment centres, also allow to focus investment in infrastructure in specific centres within countries. This is particularly important for rare cancers that require specialist diagnosis and treatment. Rare cancers represent 22% of all new cancer diagnoses in Europe, and centralisation allows earlier identification of rare molecular drivers.^{155,156} There is also evidence

- 154 Poland: Osowiecka, K., Rucinska, M., Nowakowski, J. J. and Nawrocki, S. (2018). How Long Are Cancer Patients Waiting for Oncological Therapy in Poland? *International journal of environmental research and public health*, 15(4): 577. Netherlands: Helsper, C. C., van Erp, N. N., Peeters, P. P. and de Wit, N. N. (2017). Time to diagnosis and treatment for cancer patients in the Netherlands: Room for improvement? *European Journal of Cancer*, 87, 113-121. England: Labbé, C., Anderson, M., Simard, S., Tremblay, L., Laberge, F., Vaillancourt, R. and Lacasse, Y. (2017). Wait times for diagnosis and treatment of lung cancer: a single-centre experience. *Current Oncology*, 24(6): 367. Denmark: Jensen, H., Tørring, M. L., Olesen, F., Overgaard, J., Fenger-Grøn, M. and Vedsted, P. (2015). Diagnostic intervals before and after implementation of cancer patient pathways – a GP survey and registry based comparison of three cohorts of cancer patients. *BMC cancer*, 15(1): 308; Iachina, M., Jakobsen, E., Fallesen, A. K. and Green, A. (2017). Transfer between hospitals as a predictor of delay in diagnosis and treatment of patients with Non-Small Cell Lung Cancer—a register based cohort-study. *BMC health services research*, 17(1): 267. France Pourcel, G., Ledesert, B., Bousquet, P. J., Ferrari, C., Viguier, J. and Buzyn, A. (2013). Délais de prise en charge des quatre cancers les plus fréquents dans plusieurs régions de France en 2011 et 2012. *Bulletin du Cancer*, 100(12): 1237-1250. Denmark:
- 155 Wait, S., Han, D., Muthu, V., Oliver, K., Chrostowski, S., Florindi, F., ... and Wierinck, L. (2017). Towards sustainable cancer care: Reducing inefficiencies, improving outcomes – A policy report from the All. Can initiative. *Journal of Cancer Policy*, 13, 47-64.
- 156 Van Goudoever, H. (2015). Concentrating childhood cancer treatment in the Netherlands. *Padiatrie Und Padologie*, 50(Suppl 2): 38–41. <http://doi.org/10.1007/s00608-015-0282-3>

demonstrating that centralising rare cancer care to specialist centres of excellence improves outcomes for patients.¹⁵⁷ A Cochrane analysis in ovarian and gynaecological cancers found that centralisation was associated with improved survival outcomes.¹⁵⁸ Studies have also suggested that centralisation may be associated with increased cost-effectiveness of PM. One study shows an incremental cost-effectiveness ratio of \$5,209 per QALY when comparing a centralised to a non-centralised approach.¹⁵⁹ Another study illustrates that while centralisation of ovarian cancer treatment increased costs in the short term, this investment was found to be cost-effective in the longer term (estimated at €3,616 per QALY).¹⁶⁰

Although having fewer specialised hospitals can create bottlenecks in systems (and inequities between urban and non-urban areas), countries with greater centralisation are generally smaller ones. Their size enables the countries to manage the scarcity of expertise while ensuring patient access, whereas larger countries focus on organising networks of care. Nonetheless, a key trend across all countries is the concentration of expertise to deliver treatment to ensure that PM is used rationally and effectively, particularly as PM becomes more complex and expensive (e.g. with the arrival of cell and gene therapies).

Countries should endeavour to increase coordination of care. However, how this is undertaken can vary between countries and diseases. For rare tumours, for example, countries are likely to favour centralisation. However, when medicines become standard of care, their use should shift to more general oncology centres delivering routine care for PM, under adequate guidance from ‘hub’ centres or coordinating organisations.

3.3. Access to diagnostics and testing infrastructure

The third issue identified is ensuring access to diagnostics, as PM involves the use of biomarkers to stratify patients. There are different approaches to genetic testing: germline DNA testing is the domain of clinical genetics, while tumour testing is the domain of pathology/molecular pathology. Access pathways for these diagnostics vary greatly across Europe, and this is a significant barrier to accessing PM. In order to implement PM, key elements are required in the testing environment and in the infrastructure (availability of labs, expertise, and equipment) but also in the funding and reimbursement conditions of the tests. How this is organised differs from country to country.

Figure 10 outlines the current situation for implementation of companion diagnostic (CDx) tests, which are used to determine the applicability of a therapeutic drug to a specific patient. We examine these elements in greater detail below, providing examples of how efforts have been more successful in some countries than others.

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- 157 European Union Committee of Experts on Rare Diseases. EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States 2011:13.
- 158 Woo, Y L et al. (2012). Centralisation of services for gynaecological cancer. Cochrane database of systematic reviews
- 159 Ke Ba, KM et al. (2012). The costs of centralisation: a systematic review of the economic impact of the centralisation of cancer services. *European J Cancer Care*. 12 (2).
- 160 Cole, A., Lundqvist, A., Lorgelly, P., Norrlid, H., Karlsberg Schaffer, S., Lewis, F., ... and Bianchi, S. (2016). Improving efficiency and resource allocation in future cancer care (No. 001748). Office of Health Economics.

Figure 10: Current situation regarding implementation of CDx testing in Europe



Source: CRA analysis

Focusing on molecular testing for cancer, the main classes of diagnostic methods include:

- Traditional tissue-based pathology methods such as in situ methods (e.g. immunohistochemistry (IHC) / fluorescence in situ hybridization (FISH))
- Molecular pathology methods, and increasingly multiplex molecular pathology methods like NGS
- Liquid biopsy methods from blood plasma, e.g. mutation testing from circulating cell free tumour DNA (ctDNA), which may also use multiplex NGS technology.

In general, IHC methods are widely adopted, as the method is well established in pathology, although the use of some tests may be restricted due to the types of equipment available. Newer methods such as NGS and liquid biopsy require specialist expertise and infrastructure – particularly for the bioinformatic analysis of NGS data.

Choice of assay technologies

With regard to the type of tests used by labs over time, some fragmented data is available from publications on External Quality Assessment (EQA) schemes. For example, data from UK NEQAS from 2007 to 2012 indicate an initial strong uptake of the companion diagnostic Herceptest (for HER2) when Herceptin was first introduced. There was a gradual evolution over time, with labs diversifying to a range of alternative tests. This suggests that labs may be more reliant on available companion diagnostic kits when a new test is released but over time build internal expertise and confidence to diverge into other methods, or to develop their own equivalent in-house laboratory tests.¹⁶¹

161

Han, H. S. and Magliocco, A. M. (2016). Molecular testing and the pathologist's role in clinical trials of breast cancer. *Clinical breast cancer*, 16(3): 166-179.

The lab's decision to adopt a particular test may be dependent on the reimbursement regime for diagnostics locally. For example, if NGS panels are reimbursed and single gene tests are not, this will lead to greater use of NGS. Member states' investment in logistics and technology infrastructure, in order to build local capacities and capabilities, can greatly support laboratories in their adoption of new technologies. We discuss this in further detail in section 3.3.1, with examples of national efforts for integrating NGS testing in the UK and France.

Data on uptake and access to different therapeutic tests across our case studies is presented in Table 12, based on data collected from secondary sources and validated with external and industry interviews. Despite the importance of testing, there is currently no standard metric or central public data set that shows usage of diagnostic tests in Europe with geographical breakdown, either in terms of biomarker testing performed by laboratories or in terms of the sales of commercial test kits and equipment.¹⁶² This shows significant variation across countries.

- Data are available for the UK and France; they show that test adoption for BRAF+ mutation testing in melanoma is approximately 56% (UK) and 45% (France).¹⁶³
- Across the case studies examined in this analysis, and perhaps unsurprisingly given its earlier introduction, HER2 testing is seen as having the highest uptake across Europe, followed by EGFR testing. This suggests that the length of time to adoption is long and the rate of adoption increases with the length of time that products with specific companion diagnostic needs have been available.
- While usage of NGS systems is increasing, this varies by country. Germany has been described as one of the slowest European markets to adopt: only 7% of clinical molecular diagnostic (MoDx) laboratories use NGS, and more than 50% of systems still use Sanger sequencers for oncology.¹⁶⁴ The UK has the highest NGS usage for oncology – 52% of labs. Overall, approximately 17% of MoDx labs in Europe have an NGS machine, and another 21% plan to run NGS within five years. In terms of how this translates into patient access, according to respective strategies on PM, England expects diagnostic capacity for NGS to reach 70,000 patients a year by 2020.¹⁶⁵ Similarly, France hopes to be capable of sequencing 235,000 genomes a year by 2020.¹⁶⁶

To understand this further we have considered the testing environment and funding model.

For new technologies, such as liquid biopsy mutation testing from ctDNA, the situation is still evolving. Recent data suggests that a large number of labs in Europe are evaluating

162 Where relevant, national data sources are included in the case study-specific appendices to this report
 163 Tadeu dos Santos, M. et al. (2016) International comparison of BRAF testing in melanoma. *JCO*, 34. https://10.1200/JCO.2016.34.15_suppl.e21053
 164 Whitten, C. M., Thum, A. and Blass, T. (2016). Current and future next generation sequencing usage in European molecular oncology diagnostics. *Annals of Oncology*, 27(suppl_6).
 165 NHS England. Next Steps on the NHS Five Year Forward View. Available at: <https://www.england.nhs.uk/five-year-forward-view/next-steps-on-the-nhs-five-year-forward-view/cancer>
 166 Lethimonnier, F. and Levy, Y. (2018). Genomic Medicine France 2025. *Annals of Oncology*.

the technology in a research setting.¹⁶⁷ Current clinical applications for ctDNA testing are largely confined to NSCLC and colorectal cancer (CRC), although there is potential for its use in many other areas of oncology. Recently, EGFR mutation tests have been developed that utilise this method. However, given the limited duration on the market it is difficult to draw conclusions about relative uptake.¹⁶⁸

The evidence on how the test should be used is still developing. Existing evidence suggests that the test is less sensitive in both the treatment naïve (patients who never undergone treatment for a particular illness) and progression settings when compared to tissue testing.¹⁶⁹ For this reason, treatment protocols for EGFR-TKIs state that a tissue biopsy should be considered where possible when the plasma result is negative.¹⁷⁰ Given all the challenges related to the sensitivity of the test, the need for careful blood sampling, DNA extraction protocols and clinical scenarios where ctDNA may or may not be abundant, laboratories conducting the test will need appropriate training and specialised expertise with solid verification process and external quality assurance to ensure that the test is being performed correctly.

167 Deans, Z. C., Williams, H., Dequeker, E. M., Keppens, C., Normanno, N., Schuurig, E., ... and Hall, J. A. (2017). Review of the implementation of plasma ctDNA testing on behalf of IQN Path ASBL: a perspective from an EQA providers' survey. *Virchows Archiv*, 471(6): 809-813.

168 In 2016 the FDA approved the first companion diagnostic plasma EGFR test in NSCLC for treatment with Tarceva (erlotinib) – Cobas EGFR mutation test v2 by Roche Molecular Diagnostics. In September 2017, the same test received FDA approval for resistance monitoring by detection of EGFR T790M and the use with AstraZeneca's Tagrisso (osimertinib). Karachaliou, N., Sosa, A. E., Molina, M. A., Centelles Ruiz, M. and Rosell, R. (2017). Possible application of circulating free tumor DNA in non-small cell lung cancer patients. *Journal of Thoracic Disease*, 9(Suppl 13): S1364–S1372. <http://doi.org/10.21037/jtd.2017.09.59>

169 Veldore, V. H., Choughule, A., Routhu, T., Mandloi, N., Noronha, V., Joshi, A., ... and Prabhash, K. (2018). Validation of liquid biopsy: plasma cell-free DNA testing in clinical management of advanced non-small cell lung cancer. *Lung Cancer: Targets and Therapy*, 9, 1.

170 Bernabé, R., Hickson, N., Wallace, A. and Blackhall, F. H. (2017). What do we need to make circulating tumour DNA (ctDNA) a routine diagnostic test in lung cancer?. *European Journal of Cancer*, 81, 66-73.

Table 12: Estimated uptake and access to diagnostic tests across case study markets

Indication	Diagnostic test	DK	EN	FR	NL	PL
Breast cancer	HER2	●	●	●	●	●
	BRCA 1/2	●	●	●	●	●
Melanoma	BRAF V600 mutation	●	●	●	●	●
	PD-L1	●	●	●	●	●
NSCLC	EGFR *	●	●	●	●	●
	ALK	●	●	●	●	●
	PD-L1	●	●	●	●	●
Ovarian cancer	BRCA 1/2	●	●	●	●	●
Gene panel testing	NGS	●	●	●	●	●

Notes: Green – High uptake / Full reimbursement; Amber – Medium uptake / Conditional reimbursement; Red – Limited uptake / limited reimbursement

* Includes both ctDNA testing by liquid biopsy and traditional solid tumour biopsy approaches

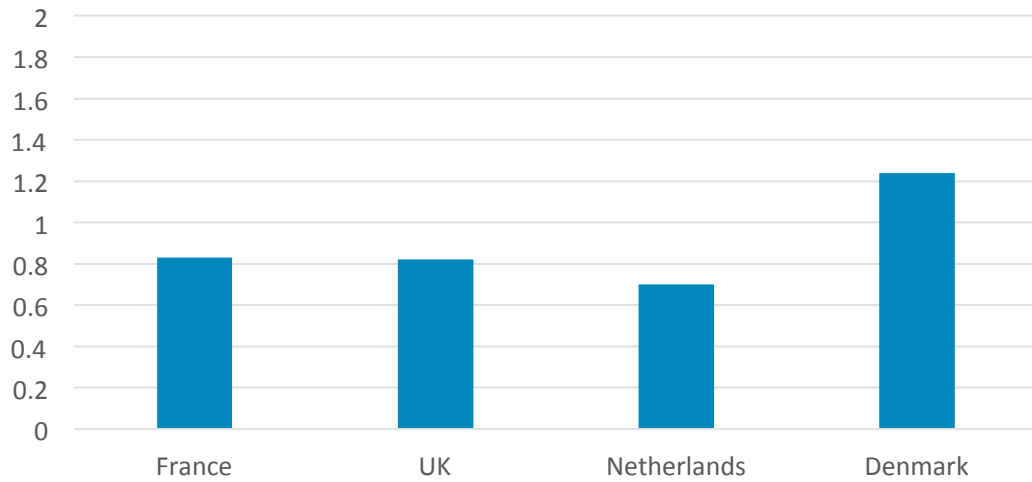
Source: CRA analysis of stakeholder interviews and EBE/EFPIA member companies' feedback

3.3.1. Testing landscape

In Europe we have seen European laboratories investing in both commercial testing platforms and in-house lab-developed tests (LDTs). Stakeholders report significant variation in how tests are performed – such as the increasing interest in using NGS in place of older IHC assays.¹⁷¹

In Figure 11, an estimate of infrastructure across case study markets is shown, using DNA diagnostic laboratories (i.e. those offering services such as NGS and Sanger sequencing) as a proxy for overall availability of diagnostic services.

Figure 11: Number of DNA diagnostic laboratories (per million population)

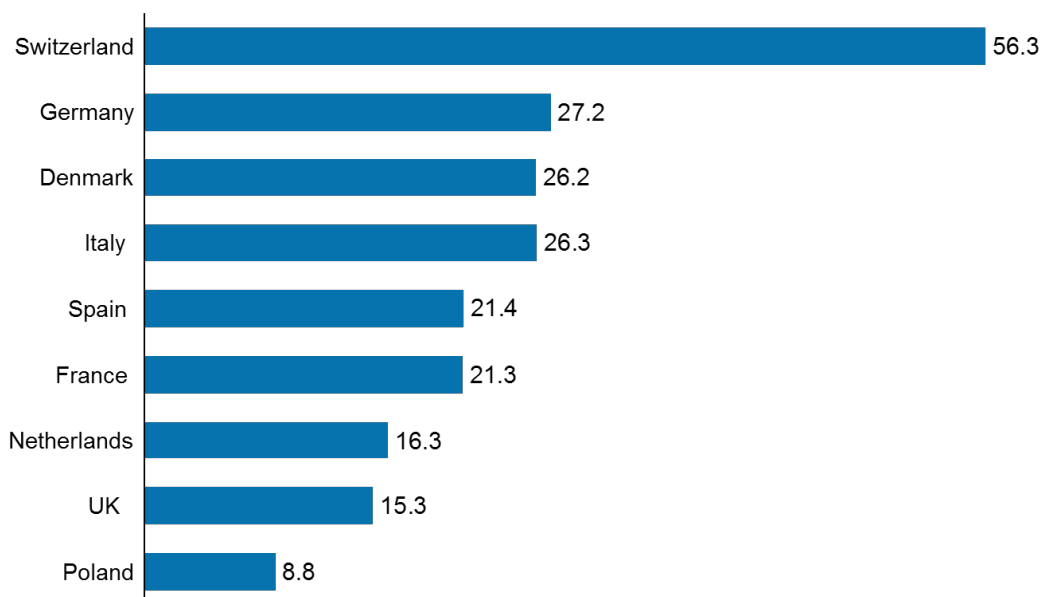


Source: European Directory of DNA Diagnostic Laboratories. No data record for Poland.

In other countries, access to diagnostic testing is limited by the testing environment. For example, a 2014 analysis commissioned by Cancer Research UK showed England had a significant gap between demand and provision for testing in some cancers, particularly NSCLC).¹⁷² However, this is improving due to changes in procurement of genomics and molecular diagnostic services.

In contrast, Figure 12 highlights the per capita expenditure on in vitro diagnostics (IVD) across selected countries in Europe, which varies widely across countries, from a low of €8.8 in Poland, to €15.3 in the UK, to the highest, €56.3 in Switzerland.

Figure 12: Per capita expenditure on in vitro diagnostics (€) (2016)



172

CRUK reports, 2015

Source: MedTech Europe¹⁷³

Funding models for diagnostic testing

Our interviewees also highlighted that one of the most significant issues for PM is that diagnostic services do not have clear funding mechanisms. The way diagnostics are funded varies depending on the therapy area and the country. This has also varied over time, and we have seen very different levels of investment by countries. It is important to differentiate between investment in testing infrastructure and investment in funding the individual tests.

As set out in Section 3.1, a number of countries in Europe, such as France and Denmark, have invested heavily in capacity building for molecular testing laboratory infrastructure. This is best illustrated by France, where since 2006 INCa has set up a national program to support molecular testing with the establishment of 28 regional molecular genetics centres. These centres provide a combination of commercially developed IVD test kits and laboratory-developed validated testing approaches. These tests are increasingly included in the reimbursement list of the social health insurance funds in France which reimburses for pathology, anatomy and cytology examinations and the NABM (Nomenclature of Acts of Medical Biology) for biology exams. Despite the specific funding of laboratories for molecular diagnostics, there appears to be limited access for specific prognostic / diagnostic multianalyte assays in France.

The Ministry of Health in France has set out the slow adoption of all diagnostics testing methods by setting targets within the biomarker platforms on specific tests.¹⁷⁴ The ministry recently introduced reforms to streamline access to diagnostics in France and force both public and private institutions to integrate the reimbursement of diagnostics in the hospital diagnosis-related group (DRG) system.¹⁷⁵ Additionally, to help facilitate access, the ministry created an innovation fund for novel diagnostics in 2015. The RIHN (Referentiel des actes innovants hors nomenclatures) provides access to conditionally approved products. To date, four molecular signatures (Oncotype DX, PAM 50, endopredict and Mammaprint) have obtained conditional access via this mechanism, and during this time the National Authority for Health (HAS) is able to assess the technology and make a final recommendation for reimbursement.¹⁷⁶ From 2016, NGS was also added to this fund.

Other countries have integrated the financing of testing services into hospital budgets which are expected to be covered through a DRG-type funding or existing block grants. This is the case in Poland, where HER2 breast cancer diagnostic testing is predominantly the responsibility of pathology laboratories in hospitals. This creates challenges for the introduction of new tests, in terms of enabling infrastructure investment as well as ensuring that existing public reimbursement rates (tariffs) are sufficient to cover the cost of a new testing approach. Specialist cancer centres in Poland – specifically the Maria

173 MedTech Europe (2016) EUROPEAN IVD MARKET STATISTICS REPORT 2016

174 Interview with French payer

175 Diagnosis-related group (DRG) is a system to classify hospital activities into groups of care activities used for budget setting and for transactions between capitated providers, and for elective surgery and similar short self-contained treatments or investigations. The system is also referred to as "the DRGs", and its intent was to identify the "products" that a hospital provides.

176 Krishnaswamy, J. (2017) 'Harmonised reimbursement approach key to reducing treatment inequalities' EU Health, Government Gazette – Health, Healthcare Policy – <http://governmentgazette.eu/?p=7434>

Skłodowska Curie Institute are active in developing methods and approaches for NGS detection of genetic abnormalities for breast cancer prognosis and diagnosis. There is also evidence of a private market for specific assays in Poland; MammaPrint, for example, is available as a privately ordered test from Polish-based laboratories.¹⁷⁷

However, until now, investment in companion diagnostics was linked to the value of an individual medicine, so that investment could be supported by the manufacturer. This occurs in many markets but is particularly important in the UK. As we move to testing that is not specific to a particular product (profiling of patients or WGS), the business case supporting this funding mechanism is no longer justified. This will lead to significant challenges for funding infrastructure in the future. A hybrid model is needed with some centralised funding and funding associated to testing for particular conditions.

Countries have adopted different approaches to funding – focusing on centralised funding (France), DRG-based approaches (England, Netherlands) and a self-pay approach in Poland. The direct funding model has been an effective enabler of PM and diagnostic testing in oncology; however, stakeholders identify two key risks with this model:¹⁷⁸

- First, the focus on oncology means that there is limited or no capacity to implement novel biomarkers in other therapy areas.
- Second, although the direct funding model results in laboratories that are highly successful in adopting novel biomarkers and in using laboratory developed testing approaches, this does not necessarily translate into effective assessment and adoption of novel commercially developed tests. In the long term, this approach may reduce incentives for manufacturers of commercial test kits, and it may negatively impact continued innovation and competition. Consequently, the associated benefits of this model– such as reduced costs over time, new technologies, and increased efficiency in genetic sequencing – could be limited.

Another key feature of European testing and funding is that it is predominantly government-supported, in terms of both infrastructure investment and funding for patient testing. There is limited evidence for mainstream use of self-paid testing services – except in the early introduction of novel biomarkers in the UK, where manufacturers pay for testing in private laboratories to support new products; or in the non-reimbursed sectors in Poland and the Netherlands (particularly for the multi-analyte gene profile tests). State investment in infrastructure is a key feature of PM in France, the Netherlands and Denmark. This contrasts with other developed nations such as Australia, where large private laboratories perform testing on a fee-for-service basis, reimbursed through the national Medicare payments system.

Funding systems also vary in the degree to which they encourage competition. Increasing investment and competition amongst technology providers has been a key enabler in the Netherlands; for example, laboratories are able to develop new techniques and increase testing capacity to efficiently deliver testing services within insurance funding (as costs have dropped in terms of per-test cost for next generation sequencing).¹⁷⁹

177 See, for example, F. Chopin Hospital (<http://www.ecz-innowacje.pl>)

178 Interviews with payers

179 Netherlands pathologist interview

Whilst the centralised funding model of some European systems may allow for infrastructure investment and high levels of access, a DRG approach using competitive fee-for-service laboratories may drive competition, lead to quicker innovation, and reduce prices, thereby improving access to PM in general. Key to enabling further competition and enabling flexible development of publicly owned services is ensuring that funding for diagnostic tests is available, that it can be effectively accessed by providers, and that it can be implemented in a similar time frame to that of access to medicines.

Both centralised funding and a tariff-based approach have a role. As we move to genetic profiling or WGS, the funding model needs to take into account the required investment in infrastructure and capacity development, as well as the need to encourage competition between diagnostic providers – but funding must also be sustainable.

Continuing to invest in next-generation testing infrastructure (such as molecular genetics labs), as well as developing dedicated funding pathways, will enable testing services to become more competitive and cost-effective over time.

3.3.2. Variation in quality of testing

The development and introduction of new technologies that allow automation of the testing process, as well as higher-throughput testing, have improved the diagnosis of diseases and patient care.

European laboratories have a significant degree of freedom in choosing how to implement biomarker testing. Personalised medicines in Europe are authorised by EMA with indications that identify oncogenic or germline mutations but do not specify a particular testing technology, approach, or commercially available test product. Thus, a key feature of PM in Europe is that whilst products require the identification of patients through biomarkers and increasingly complex genetic profiling, specific tests are currently not tied to product authorisation.¹⁸⁰ This contrasts with the US approach, where FDA approval of a new drug may include one or more specific assays or commercial test kits.¹⁸¹

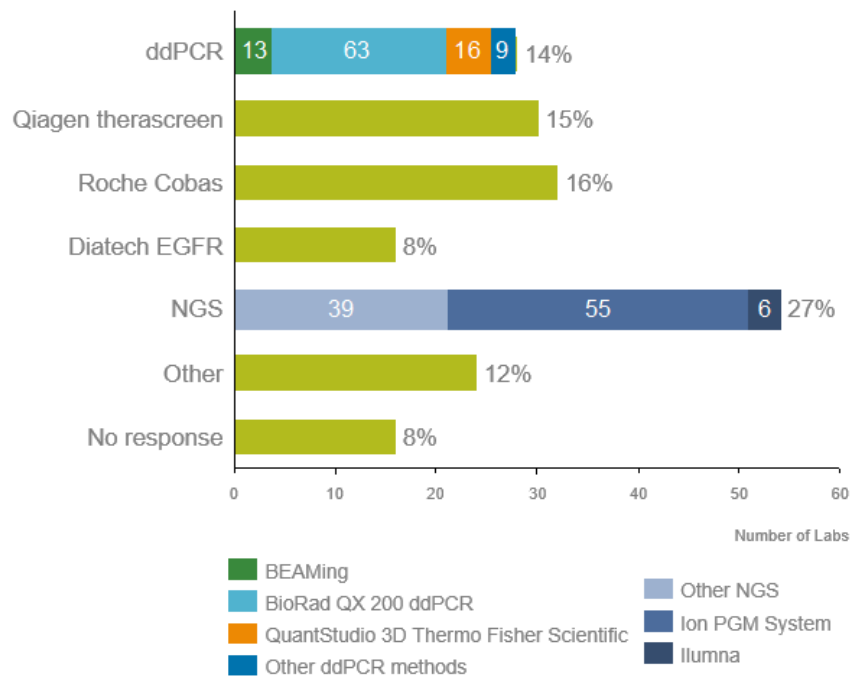
Studies show that clinical laboratories across Europe are using various methods, with different limits of detection for mutation testing, for diagnosis. For example, a recent survey reviewed the implementation of plasma ctDNA testing in Europe, looking specifically at current practice for plasma ctDNA testing in CRC and NSCLC tumour diagnostic.¹⁸² As shown in Figure 13, the most frequently used method for plasma ctDNA testing was NGS, used by 27% of laboratories. Of the laboratories using more than one plasma ctDNA testing method, 90 (54%) employ a single method, 51 (31%) use two, and 8 (5%) use three different methods. This may result in variation in the quality of testing results.

¹⁸⁰ Current market entry conditions for IVD (in-vitro diagnostic) devices may be subject to change following the adoption of the IVD directive (Regulation (EU) 2017/746) in April 2017

¹⁸¹ See, for example, FDA public information on companion diagnostics and personalised medicine approvals, <https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm407328.htm>

¹⁸² Deans, Z. C., Williams, H., Dequeker, E. M., Keppens, C., Normanno, N., Schuurig, E., ... and Hall, J. A. (2017). Review of the implementation of plasma ctDNA testing on behalf of IQN Path ASBL: a perspective from an EQA providers' survey. *Virchows Archiv*, 471(6): 809-813.

Figure 13: Most frequently used methods for plasma ctDNA testing



Source: IQN Path

Such variations in testing approach may create inconsistencies both within and across countries. Multiple factors may be influencing the quality of diagnostic (Dx) testing, resulting in inconsistent laboratory/test performance. There is little evidence base for recommendations on testing methods and how to improve testing quality. There is limited public information on lab performance or test usage. Interviewees argued that until local services can validate and embed testing in patient pathways, laboratory and clinical uptake of plasma ctDNA may be hindered. The delivery of National and International EQA schemes is essential to maintaining quality, and this will also require greater transparency regarding performance. Some interviewees noted that addressing this challenge may require effective national and potentially international guidelines for the use, development, and implementation of testing. This may include shared standards for quality assurance and competency testing specifically for pathology services, as a key enabler of PM.

In many countries, the compliance requirement around implementation of quality reporting could be improved. EQA schemes have been adopted as a mechanism for ensuring that testing remains at a given quality standard. Laboratories must provide high-quality testing services in which clinical teams and patients have confidence.

A further key policy challenge for PM in Europe is the availability of high-quality data on testing and the use of diagnostic technologies. Whilst national-level biobanks and clinical registries may provide some data for research purposes, there are no shared standards, and in some cases (notably in Denmark) such registries are further fragmented into tumour-specific records. Manufacturers wishing to understand the real-world use of particular technologies, as well as clinicians tracking patient outcomes over time, could use high-quality data on patients and testing to clarify how countries are implementing and adopting personalisation, as well as enable analysis at sub-national level. Whilst

national reports in the UK (particularly as enabled through the work of Cancer Research UK) and NHS statistic¹⁸³ and summary statistics in France (generated by INCa) provide some insight into testing rates, robust and accessible data on testing rates and test usage, in particular, appears to be a key gap for both health systems and for manufacturers of PM.¹⁸⁴ Although there are some industry-sponsored projects which aim to improve the collection of data in oncology to move beyond tumour-type silos, such efforts are still limited to oncology. As PM expands beyond cancer, other therapy areas will still need to 'catch up' on data to monitor the use of diagnostics and PM.

There is currently a lack of information on testing methods and clear data on diagnostic uptake, as well as poor oversight on the performance of labs. Collecting data and putting a greater emphasis on harmonised External Quality Assessment schemes (EQA) of lab will help to ensure consistent testing quality throughout Europe and allow comparison between approaches

3.3.3. Value assessment for diagnostics

The degree to which diagnostics are subject to a value assessment and the degree to which they are integrated with the assessment of associated therapies varies across Europe.

For example, in France before routine available, with possible reimbursement by the National Health Insurance Fund, they are subject to a medico-economic assessment by HAS. Furthermore, the Biomedicine Agency participates in defining the legal framework, medical guidelines for good practice, and activity evaluation. Biomarkers can be included in INCa testing practices without specific reimbursement or evaluation, but these are generally laboratory-developed biomarker tests, rather than a specific device or commercial test kit.¹⁸⁵

In the UK, tests can be evaluated by NICE for routine commissioning; to date, tests have been considered separately from products only for the commercial gene expression profiles.¹⁸⁶ However, the evaluation of diagnostics (including impact on costs) is integrated into the NICE appraisal of PM.

A balance needs to be struck between an integrated approach assessing the cost of diagnostics and medicines together and a flexible approach that incorporates new approaches (e.g. NGS).

3.4. Access to personalised medicines

The fourth issue identified is the ability for patients to access specific personalised medicines so the benefits can be realised. It is often the case that new molecular entities in oncology that are approved initially in the US (based on FDA approval, often using one of the accelerated review pathways available to manufacturers in the US) are

183 The NHS Atlas of Variation in Diagnostic Services November 2013 Reducing unwarranted variation to increase value and improve quality

184 Large market research organisations such as Ipsos MORI also have statistics on diagnostics use. These are not publicly available.

185 French payer interview

186 NICE (2013). Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management. <https://www.nice.org.uk/guidance/dg10>

subsequently approved in Europe by the EMA.¹⁸⁷ However, before medicines can be made accessible to patients, they need to go through the pricing and reimbursement process. There are therefore a number of dimensions to access and uptake:

- The mechanism of value assessment and HTA methodology applied to PM
- The degree to which medicines are reimbursed, rejected, or only reimbursed with significant constraints
- The length of time it takes to complete the price and reimbursement process (and whether there is an early access programme)
- The role and importance of guidelines in uptake, and how quickly these are updated to reflect new medicines
- The funding pathways and allocated investment in PM.

3.4.1. Value assessment and reimbursement

All of the case study countries, except Denmark, apply HTA systematically to PM. The HTA system is a significant barrier to the reimbursement of innovative medicines in Europe, though HTA bodies have reacted differently to assessing innovative targeted therapies:

- In France, the Transparency Commission conducts a relative efficacy assessment based on an appropriate comparator (standard of care). Most of the indications of targeted therapies for cancer that have been evaluated have received a favourable opinion by HAS, and three quarters of them have demonstrated improved clinical benefits over the standard of care i.e. an ASMR I-IV (amélioration du service médical rendu).¹⁸⁸
- In England, access to personalised cancer treatments has faced numerous challenges in meeting cost-effectiveness thresholds to achieve positive NICE recommendations. Consequently, all recently approved innovative medicines required some form of patient or managed access scheme to reduce their costs to within accepted thresholds.

The situation is changing in some markets. Previously, Denmark did not apply HTA to innovative medicines, but in June 2017 the Medicines Council started assessing whether new medicines, and existing medicines with new indications, should be recommended for the five Danish hospital regions. Without a recommendation from the Medicines Council, hospital medicines will likely not be used in Denmark. As a result, the time between approval and access in Denmark is likely to increase significantly in the coming years, as the Medicines Council will consider benefit in relation to price, and will negotiate discounts.¹⁸⁹ Nonetheless, in December 2017 the Medicines Council recommended nivolumab, atezolizumab and pembrolizumab for the treatment of urothelial cancer.¹⁹⁰

187 Johansson, T. (2016) Europe vs USA: new drug product approvals in 2016, NDA Group, available at <http://www.ndareg.com/europe-vs-usa-new-drug-product-approvals-in-2016/>

188 HAS/INCa 2015

189 Office of Health Economics (2016). "Improving Efficiency and Resource Allocation in Future Cancer Care."

190 Medicines Council. Recommendations – new drugs and new indications. Available at: <http://www.medicinraadet.dk/anbefalinger-og-vejledninger/anbefalinger-nye-laegemidler-og-nye-indikationer>

According to our interviews, payer perceptions of products with companion diagnostics or specific biomarkers are generally more positive than of those without such biomarkers.¹⁹¹ Payers see the use of biomarkers as a way of reducing risk; i.e. by increasing the likelihood that benefits seen in clinical trials will translate into benefits in day to day clinical practice. In fact, a study has reviewed the impact of currently available predictive biomarkers on HTA in the context of the agencies' evidence requirements in five treatment areas: HIV, gastrointestinal stromal tumour (GIST), NSCLC, CRC, and breast cancer.¹⁹² The study finds that biomarkers such as HER2 and KRAS had a high impact in all included submissions, with 100% and 75% respectively resulting in positive recommendations. In contrast the EGFR biomarker had a lower impact (not mentioned in 4 out of 10 submissions); 60% of these submissions were approved and 40% rejected. For those submissions where the biomarker impacted highly on the HTA decision, accuracy was a major influence. For example, cetuximab was rejected in England when submitted in association with EGFR but accepted when linked with KRAS, a biomarker with more accurate predictive power.

Looking at the reimbursement of PM (as of March 2018) presented in Table 13, countries like England with more strict HTA methodology and cost-effectiveness thresholds experience more restricted reimbursement and access to PM, in contrast to Denmark¹⁹³ and the Netherlands. Poland is more likely to restrict access to manage budget impact.¹⁹⁴

191 English and France payer interview

192 Trevor, N. C. and Alnwick, K. (2010). PHP105 How can the use of predictive biomarkers lead to positive HTA recommendations? *Value in Health*, 13(7): A423-A424.

193 Most PM in Denmark go through the Use of Expensive Hospital Medicines (RADS) and "Koordineringsrådet for ibrugtagning af sygehusmedicin" (KRIS) which supports the Danish Medicines Council in approving reimbursement of medicines. KRIS have now established a working group to investigate bio marker (currently with focus on PD-L1) in order to restrict access as much as possible by biomarker, as well as promote the use of competitive tenders in hospitals.

194 Jahnz-Różyk, K., Kawalec, P., Malinowski, K. and Czok, K. (2017). Drug policy in Poland. *Value in health regional issues*, 13, 23-26.

Table 13: Reimbursement status of PM across case study markets

Indication	Class	Drug	DK	EN	FR	NL	PL
Breast cancer	HER2+	Trastuzumab (Herceptin)	●	●	●	●	●
	HER2+	Lapatinib (Tyverb)	●	●	●	●	●
	HER2+	Pertuzumab (Perjeta)	●	●	●	●	●
	HER2+	Ado-trastuzumab emtansine (Kadcyla)	●	●	●	●	●
Melanoma	BRAF+	Vemurafenib (Zelboraf)	●	●	●	●	●
	BRAF+	Cobimetinib (Cotellic)	●	●	●	●	●
	BRAF+	Dabrafenib (Tafinlar)	●	●	●	●	●
	BRAF+	Trametinib (Mekinist)	●	●	●	●	●
	CTLA-4	Ipilimumab (Yervoy)	●	●	●	●	●
	PD-1	Pembrolizumab (Keytruda)	●	●	●	●	●
	PD-1	Nivolumab (Opdivo)	●	●	●	●	●
NSCLC	EGFR+	Gefitinib (Iressa)	●	●	●	●	●
	EGFR+	Erlotinib (Tarceva)	●	●	●	●	●
	EGFR+	Afatinib (Giotrif)	●	●	●	●	●
	EGFR+	Osimertinib (Tagrisso)	●	●	●	●	●
	ALK+	Crizotinib (Xalkori)	●	●	●	●	●
	ALK+	Ceritinib (Zykadia)	●	●	●	●	●
	ALK+	Alectinib (Alecensa)	●	●	●	●	●
	PD-1	Pembrolizumab (Keytruda)	●	●	●	●	●
	PD-1	Nivolumab (Opdivo)	●	●	●	●	●
	Ovarian cancer	VEGF-A	Avastin (bevacizumab)	●	●	●	●
PARP		Lynparza (olaparib)	●	●	●	●	●

Notes: Green – Full reimbursement; Amber – Reimbursed with restrictions; Red – Limited / no reimbursement

Source: CRA analysis

Challenges with current HTA methodologies for PM

The emergence of PM (particularly in oncology) has prompted profound changes in clinical trial design and led to a reconsideration of the drug approval process. Regulators have been under pressure to speed up approval for certain types of products and to develop a flexible approach that ensures patients have rapid access to innovative medicines whilst also ensuring that the regulatory process continues to be based on adequate evidence regarding the safety and efficacy of new treatments.¹⁹⁵ The EMA

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Eichler, H.G., Baird, L.G., Barker, R., Bloechl-Daum, B., Børlum-Kristensen, F., Brown, J. and Garner, S. (2015). "From adaptive licensing to adaptive pathways: delivering a flexible life-span approach to bring new drugs to patients." *Clinical Pharmacology and Therapeutics*, 97(3): 234-246.

focused on expedited drug approval programmes based on conditional approval and has become more flexible in accepting phase II single-arm trials instead of full randomised control trials. Since 2003, a number of oncology PM have gained marketing authorisation with phase II single-arm studies or phase III with limited and immature data. From the list of 21 PM in Table 13, 4 were approved through a conditional authorisation with phase II single-arm trial only or with immature data. Given the increased fragmentation of treatment populations and the challenges this brings to clinical trial design, this number is expected to increase in the future.

Unlike the regulators, payers must balance uncertainties about the net benefits of treatments with their financial costs and forgone alternative treatment opportunities. Early access decisions are challenging from a reimbursement perspective, due to the limited evidence available to conclude on the benefit–risk and relative (cost-) effectiveness of new cancer drugs. While medicines regulators have been willing to accept phase II single-arm trials as part of expedited drug approval schemes, HTA bodies and payers continue to see large, comparative randomised clinical studies as the gold standard. HTA bodies and payers have not been as receptive to the use of non-randomised controlled trial (RCT) evidence in HTA submissions; they often request large phase III RCTs,¹⁹⁶ ideally with a comparator, and in general disregard the use of non-RCT evidence. In addition to favouring RCTs, they also favour primary endpoints, such as overall survival (OS). Overall response rate (ORR) is usually the endpoint of a single-arm trial and shows clear efficacy data, which has been enough for regulators. However, payers like to see the OS, which can only be attained through a trial designed with a comparator arm.

The history of products gaining regulatory approval on products with immature clinical data (e.g. conditionally approved products with phase II data only) varies from country to country. According to interviews, the environment in France has become less receptive. In contrast, developments in England with regards to the Cancer Drug Fund (CDF) and the use of coverage with evidence developments is seen as becoming more progressive (described below). The result is that while the EMA has become more ‘adaptive’ and willing to accept phase II single-arm trials, only some European HTA bodies and payers have changed their evidence expectations.¹⁹⁷ This ‘misalignment’ creates a gap between regulators and HTA bodies/payers when approving and evaluating reimbursement for new therapies.¹⁹⁸

A better alignment of data requirements between HTA bodies and regulators could mitigate the challenge of additional real-world evidence (RWE) requirements. Several initiatives and projects have emerged to address this gap, including parallel scientific advice consultation between the EMA and HTA bodies, and Medicines Adaptive Pathways to Patients, and accelerated pathways viewed as a continuum to bring together input from all stakeholders.

196 Randomised controlled trials – where some patients are given the treatment that is being tested and others get a ‘control’ substance for comparison – became the gold standard of drug testing because they were the most effective way of seeing if a drug worked.

197 It is currently unclear if HTA bodies and payers generally have become less flexible or have stayed the same. This is an area where further analysis would be useful.

198 Martinalbo, J., Bowen, D., Camarero, J., Chapelin, M., Démolis, P., Foggi, P. and Oliveira, J. (2015). “Early market access of cancer drugs in the EU.” *Annals of Oncology*, 27(1): 96-105.

Registries and use of real-world evidence

One solution to large randomised phase III clinical trials not being available for HTA bodies and payers is the development of RWE collection. For example, patient registries are already in use in some countries; these collect real world data on a product's effectiveness, keep track of patients who are using conditionally approved products, and support ongoing clinical assessment. In addition, the UK regulator (the MHRA) has introduced the 'early access to medicines scheme' (EAMS) which allows access to medicines pre-marketing authorisation with the ability to collect real world data to support subsequent HTA.

Population-based registries have been a key enabler for reimbursement and access to PM across countries. For example, the Dutch Minister of Health made reimbursement of the first personalised treatment for melanoma conditional on the set-up of this population-based registry and centralisation of care. Consequently, the Dutch Melanoma Treatment Registry was set up in July 2013 to assure the safety and quality of melanoma care in the Netherlands.¹⁹⁹ The quality performance indicators demonstrated that the BRAF inhibitors and PD-1 inhibitors have been safely introduced in the Netherlands with toxicity rates that were consistent with the phase III trials conducted.²⁰⁰ Data captured in these registries is used for benchmarking and outcomes research, to obtain insights into real-world cost-effectiveness of treatment pathways to improve health decision making.²⁰¹

Conditional reimbursement schemes through managed entry agreements

Another key barrier to access to new innovative PM is a lack of pricing contracts that are sufficiently flexible that they can account for clinical uncertainty. Managed entry agreements remain attractive for some oncology products where HTA bodies or payers are not convinced that the evidence from clinical trials data represents real-world patient care. Schemes such as Sweden's 'coverage with evidence development', which links reimbursement to the development of additional evidence, are especially relevant for oncology products that demonstrate health outcomes in stratified patient populations.

For products that are subject to an outcomes-based agreement, HTA bodies often ask manufacturers to collect additional data as part of the conditions for approval. Currently, these schemes require manufacturers to collect evidence but do not always allow price increases if the collected data supports an increase in price. It is important that the infrastructure to collect RWE meets a high standard so HTA and payers accept the data. Current data is low quality and sporadic, because collecting RWE is a relatively new practice that still needs time to show its potential.

Other examples include hypothecated funds providing reimbursement during evidence development, as is the case with the CDF in England. Collection of RWE is important in order to facilitate interim reimbursement arrangements through the CDF, preventing the

199 Dutch payer interview

200 Jochems, A., Schouwenburg, M. G., Leeneman, B., Franken, M. G., van den Eertwegh, A. J., Haanen, J. B., ... and Blokx, W. A. (2017). Dutch Melanoma Treatment Registry: Quality assurance in the care of patients with metastatic melanoma in the Netherlands. *European Journal of Cancer*, 72, 156-165.

201 Franken, M., Leeneman, B., Schouwenburg, M., Jochems, A., Wouters, M., Van den Eertwegh, F. ... and Uyl-de Groot, C. (2015). The Dutch Melanoma Treatment Registry As Blueprint For Using Registry Data To Improve Health Care Decision Making. *Value in Health*, 18(7): A491.

formal HTA assessment from acting as a barrier to patients accessing innovative PM. An example of this agreement exists for nivolumab for NSCLC, with data collection anticipated to conclude by June 2019.²⁰²

3.4.2. Speed of access

While there are no specific rules for PM, as they often target groups of patients with high unmet need, our interviewees suggested this often leads to some of these patient being treated preferentially.²⁰³ For example, in the case of a cancer patient with no treatment alternatives, it is not considered acceptable to wait six months for a reimbursement decision on a new treatment that offers the potential to extend the patient's life by two to four months.²⁰⁴

Once there is a reimbursement decision, however, the uptake of medicines is often determined by the incorporation of PM into clinical guidelines. Treatment guidelines are used differently across EU markets; in countries such as France and Germany, physicians retain significant discretion and can prescribe any product authorised in that market. In consensus-driven markets such as Denmark, clinical guideline development is crucial for the introduction of novel therapies, as the evolution of treatment guidelines and standards represents a shared clinical agreement on care standards rather than an imposed restriction on what products can and cannot be used.²⁰⁵ In England and Poland, clinical guidelines are more integrated into HTA and product access settings, respectively. Given the different roles of guidelines, the importance of speedy publication of national rules varies from market to market and we need to be cautious in drawing conclusions.²⁰⁶

In the appendix we have examined the speed of access and uptake, drawing on the speed of reimbursement and how quickly novel products are reflected in treatment guidelines. We use examples from first-in-class personalised oncology medicines that have been approved within the last 10 years.²⁰⁷ In lung cancer, France has the fastest access to novel targeted treatments. For other conditions, such as melanoma and ovarian cancer, patients in Denmark and the Netherlands have had faster access to targeted therapies (see time to reimbursement in Figure 14), whereas in France, England and Poland this has been significantly slower; occurring at least six months after EMA approval. As illustrated in Figure 14, updates to treatment guidelines and care pathways vary across countries; however, they are generally quicker in countries where guidelines play a more important role in enabling access (i.e. Denmark and Poland).

An important determinant of access is the introduction of early access schemes in several countries (as set out in Table 14), designed to allow patients to receive access to these medicines several months before the official EMA approval. Access in France has been largely facilitated by the French ATU system. In the past decade, almost half of targeted therapies were available through a cohort ATU, granted on average 160 days before the

202 NICE: Cancer Drugs Fund – Data Collection Arrangement for nivolumab for previously treated NSCLC
203 Interviews with payers

204 Eurordis (2011) Position Paper: Patients' Priorities and Needs for Rare Disease Research 2014-2020
205 Danish local payer interview

206 It was also noted that international guidelines play an important role in the use of PM – such as the European Society for Medical Oncology or the National Cancer Centre Network in the US – can influence physician use of certain targeted medicines but are not determinative.

207 gefetinib; crizotinib; vemurafenib; pempolizumab; olaparib.

marketing authorisation (MA).²⁰⁸ Similarly, Denmark has been seen as a receptive market for targeted therapies, with early national cancer plans acknowledging the contribution of targeted cancer drugs.²⁰⁹ In contrast, access to personalised medicines in England has faced numerous challenges to meeting required cost-effectiveness thresholds to achieve positive NICE recommendations. However, more recently launched targeted therapies have benefited from the introduction of the ‘early access to medicines scheme’ (EAMS), launched in 2014. The use of pembrolizumab in melanoma was the first product to be launched through EAMS, providing over 500 UK patients with early access.²¹⁰

Table 14: Selected early access programme for personalised medicine

France	The ‘autorisation temporaire d’utilisation’ (ATU) was introduced to allow patients with an unmet clinical need to receive early access to drugs that had not yet received MA. ²¹¹
England	The early access to medicines scheme (EAMS) aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. ²¹²
Italy	Law 648/96 allows access to medicines that do not have marketing authorisation in Italy if certain conditions are met.

Source: CRA analysis

As shown in Table 15 below, nearly all PM indicated for NSCLC have benefited from early access programmes in France (via ATU scheme) or in the UK (via EAMS).

208 Institute national du Cancer (2016) Les Thérapies Ciblées dans le traitement du Cancer en 2015/État des lieux et enjeux. JUILLET 2016

209 “The long-term financial consequences of breast cancer: a Danish registry-based cohort study”
<https://bmcpublihealth.biomedcentral.com/track/pdf/10.1186/s12889-017-4839-x?site=bmcpublihealth.biomedcentral.com>

210 UK Government, 23 December 2015. Over 500 UK patients gain early access to new melanoma treatment
 211 Temporary authorisation of use, ANSM, 2017. Available at:
<http://www.ansm.sante.fr/Mediatheque/Fichiers/Activites/Autorisations-temporaires-d-utilisation>

212 Office for life sciences England (2018). EAMS. Available at: <https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eams-how-the-scheme-works>.

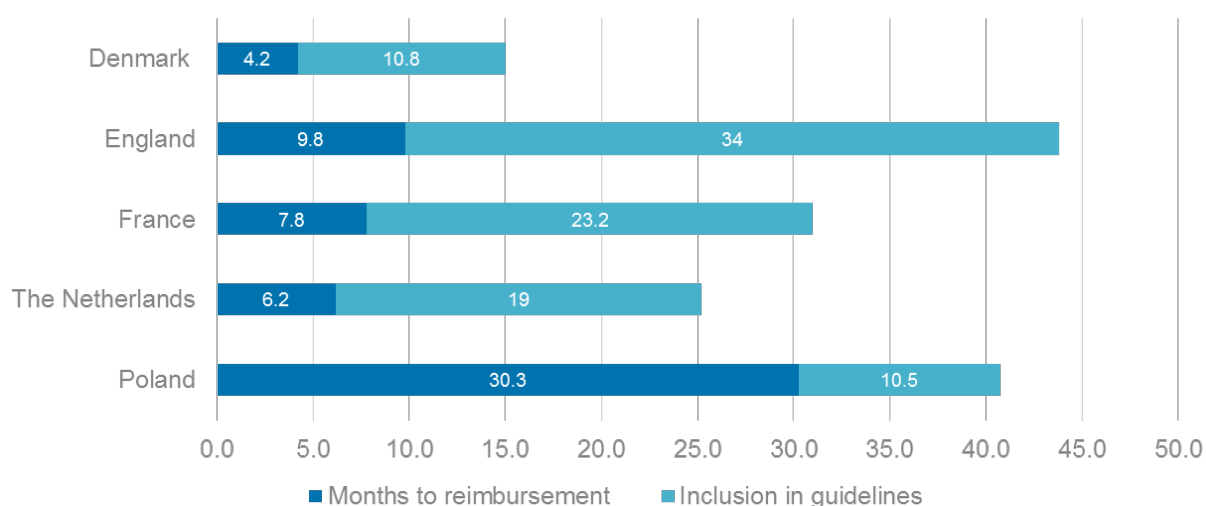
Table 15: PM for NSCLC that have benefited from early access programmes (France's ATU and England EAMS)

Indication	Class	Name	EMA Approval	FR - ATU	UK - EAMS
NSCLC	EGFR+	Gefitinib (Iressa)	June 2009	March 2004	n/a
	EGFR+	Erlotinib (Tarceva)	September 2005	April 2005	n/a
	EGFR+	Afatinib (Giotrif)	September 2013	no	no
	EGFR+	Osimertinib (Tagrisso)	February 2016	September 2015	December 2015
	ALK+	Crizotinib (Xalkori)	November 2012	November 2010	n/a
	ALK+	Ceritinib (Zykadia)	May 2015	September 2014	n/a
	ALK+	Alectinib (Alecensa)	February 2017	No	September 2017
	PD-1	Pembrolizumab (Keytruda)	July 2015	March 2015	March 2015
	PD-1	Nivolumab (Opdivo)	June 2015	May 2015	February 2016

Source: CRA analysis

It is clear that access to PM depends on

- (1) The existence of early access mechanisms that recognise the importance of PM in delivering benefits where there are unmet needs.
- (2) An effective approach to HTA. Countries that have a more pragmatic approach to use of evidence (or requirements for additional data collection) to assess the relative benefit of new PM exhibit faster access.
- (3) A fast process for updating treatment guidelines and care pathways. Although this varies depending on the role of clinical guidelines, it clearly has an important impact on enabling access in countries such as Denmark and Poland.

Figure 14: Average access timeline for personalised oncology medicines

Notes: Average access timeline from first-in-class PM in NSCLC, melanoma and ovarian cancer (gefetinib; crizotinib; vemurafenib; pembrolizumab; olaparib)

Source: CRA analysis

3.4.3. Funding pathways for PM

Finally, there are no PM-specific funding pathways. In most countries, the pricing and reimbursement mechanism depends on whether the treatment is provided in the hospital setting or in ambulatory care.

In hospital settings, prices are generally negotiated directly with the hospital purchasing group and reimbursed as part of a DRG system. However, some countries have introduced separate reimbursement lists and funding for 'high cost medicines'. In France for example, most PM are reimbursed via the innovative drugs 'liste en SUS' that includes special funding for high-cost medicines to be accessed outside of the hospital DRG systems.²¹³ This facilitates access to these therapies as the budget is more flexible and medicines on this list are fully reimbursed when prescribed according to the 'good use contract'. All targeted therapies for hospital use are on the list (except one). Similarly, in the Netherlands, separate funding has been available since 2012 for medicines indicated by the Dutch Healthcare Authority (NZA).²¹⁴ These expensive medicines can be declared separately by hospitals (outside of the DBC tariff – the dutch case-mix office - DBC-Onderhoud) to ensure full reimbursement. These medicines are called 'add-ons'. Hospitals and insurers often negotiate a budget cap for add-on medicines, which can be against the full budget or on a per-product basis.²¹⁵ In Denmark, the regional authorities are responsible for controlling and managing the hospital sector, including deciding which pharmaceuticals and diagnostics to use. The regions buy all hospital pharmaceuticals and medical devices through public tendering. Public tenders are carried out by Amgros, which is a hospital purchasing agency owned by the five regional authorities.²¹⁶

In an ambulatory setting, countries differ with regard to the reimbursement and funding system. In France, only drugs dispensed on an outpatient basis (pharmacy and retrocession) and the drugs listed on the 'liste en SUS' are subject to negotiation between CEPS and pharmaceutical companies when it comes to pricing the drug. In England, special ring-fenced funding provides a temporary fix for the issue of negative NICE guidance for innovative cancer medicines where there is uncertainty in the data. The CDF was initially established in 2011 as a source of direct funding for drugs that could not be funded through routine commissioning, though in April 2016 this changed to an interim funding scheme via managed access arrangements (as described above).

Budget impact and affordability remains a key challenge for PM. This is notable in Poland. It is likely that the next wave of innovation in personalised oncology treatment – particularly the chimeric antigen receptor T-cell (CAR-T) technologies – will add further pressure to budgets. Manufacturers and payers need to find ways to ensure that value assessments lead to prices negotiations that reward valuable innovations whilst ensuring that patients can access new medicines and can afford to pay for them.

213 Pharmaceutical drugs eligible for separate reimbursement in addition to DRG rates are listed in the liste en sus
214 WHO (2009) Pharmaceutical Health Information System PHIS Hospital Pharma Report, the Netherlands
215 Dutch payer interview
216 Amgros. <http://www.amgros.dk/en/about/about-amgros/>

3.5. Summary of country performance: enablers and barriers to PM

Looking across the five countries, we can assess their performance on the nine factors affecting the environment for PM. We find the best environments for PM in Europe are France and Denmark.

The French policy to prioritise cancer care through its National Cancer Control Plan (Plan Cancer) has created a very favourable environment which ensures the uptake and adoption of PM. However, as a result, this ongoing commitment has been largely focused on cancer care. Nevertheless, France's cancer plan has ensured continuous financial commitments to support some key objectives in optimising cancer care such as promoting early diagnosis and testing. This has allowed France to lead the way in the development of personalised medicine.

Denmark has also developed an environment very favourable to the uptake and adoption of PM in oncology. The establishment of the DMCGs promotes research coordination and collaboration, monitoring cancer care, disseminating knowledge, and creating clinical guidelines for diagnosis and treatment. The policy prioritisation of developing infrastructure for PM will no doubt help further streamline future diagnostic and testing services.

The Netherlands is a very receptive environment for the introduction of innovative therapies. The access and reimbursement system has a very pragmatic approach to value assessment, as demonstrated by the introduction of registries to monitor RWE generation of targeted therapies. This facilitates relatively fast patient access to innovative therapies with limited restrictions. However, the Netherlands lacks a forward-looking strategic approach to PM that recognises its specific value and clinical application. Relative to other European markets, there has been more limited investment in infrastructure that improves diagnostic capacity and harnesses the efficiencies of novel technologies.

In contrast, access to PM for oncology in England is mixed. There have clearly been challenges in meeting cost-effectiveness thresholds by NICE, and while mechanisms such as patients' access schemes and the Cancer Drugs Fund have facilitated access, this has led to distorted funding for personalised medicines in oncology, and uncertainties regarding how these products will be reimbursed in the future. From a policy perspective, the NHS is clearly focusing on integrating genomics and diagnostics across its services for maximum impact on patient outcomes. Improving infrastructure across a very large system will likely lead to diagnostic services becoming better organised and coordinated across the NHS.

Despite funding remaining a core challenge for enabling access to novel treatments in Poland, there has been progress through the introduction of national therapeutic plans and care pathways. As reforms to the healthcare system create more explicit centres of excellence and designated specialised centres, concentration of expertise, funding, and infrastructure may enable more use of PM. However, in order to effectively and in a timely manner harness the benefits provided by PM in a constrained system, Poland requires overarching healthcare strategies that focus specifically on PM. Through the implementation of policies that aim to develop the diagnostic environment and appreciation of associated efficiencies offered by new technologies, this may in turn enable funding to be allocated to innovative personalised treatments, improving access for Polish patients.

Table 16: Assessment of the environment for PM across Europe














Environment for Personalised Medicines	DK	EN	FR	NL	PL
Policy prioritisation					
Care environment					
Diagnostic testing infrastructure					
Uptake of diagnostics					
Mechanism of value assessment					
Use of real-world evidence					
Speed of reimbursement					
Speed of updating guidelines					
Funding and investment					

Source: CRA analysis

We summarise in Table 17 below some key enablers and barriers that have been identified throughout this report.

Table 17: Summary of enablers and barriers to the adoption of PM in Europe

Barriers	Countries
Insufficient diagnostic testing capacity or poor quality labs limits use of novel tests	
Delays or restricted reimbursement/ access for novel personalised medicines	
Lack of specific recognition of PM in value assessment guidelines	
Delays to access and updating treatment guidelines to reflect innovative treatments	
Limited level of physician exposure to current research and treatment trends	
Lack of inclusion of mutation testing in clinical guidelines	
Restrictions on funding for specific high-priority therapy areas (particularly oncology) limits applicability beyond oncology	
Funding availability or lack of clarity leading to insufficient funding of testing services	

Enablers	Countries
Development of a specific plan or strategy on PM with dedicated investments in novel diagnostic technologies	  
Highly specialised and coordinated management of care (including testing infrastructure and expertise)	 
Availability of high quality testing platforms and technologies, supported by quality assessment protocols	
Inclusion of PM in guidelines promotes usage and reflects the development of clinical consensus to support PM	 
Early access schemes that favour PM	 
Clear funding and value assessment mechanisms for diagnostic products, and the alignment into the assessment of medicines	
Interim funding mechanisms that allow for outcomes-based managed entry agreements	 

Source: CRA country analysis ( Denmark,  England,  France,  the Netherlands and  Poland)

4. Conclusion and policy recommendations

In Chapter 2 we showed that there is considerable evidence of the benefits for patients, clinicians, the healthcare system and the wider clinical development process in Europe. This is supported by evidence from stakeholder interviews and in terms of empirical evidence, although it is clearly stronger in the US than in Europe. Drawing on the case studies and the wider literature as well as input from the external interviews, we have developed a set of five recommendations on what is needed to incentivise the development of PM in Europe and to improve equitable access to PM.

1. A coherent PM strategy is a key enabler to the uptake of personalised medicine. **A national policy to ensure prioritisation of PM should work hand in hand with existing health strategic plans** (e.g. National Cancer Plans). **The level of resources and funding needs to be aligned to aspirations.** A coherent PM strategy should articulate the genomic profiling strategy in terms whether to screen more patients using a broad targeted gene panels rather than fewer patients with whole genome assays.
2. **Continued emphasis is needed on better management of care, consolidating expertise and resources to ensure the adequate ‘personalisation of care’.** This can be achieved through a centralised approach (i.e. developing ‘centres of excellence’) or via cross-functional collaboration through healthcare networks. This will allow more coordinated management of the testing infrastructure and expertise.
3. **National governments should continue investing and cooperating in next-generation testing infrastructure (such as molecular genetics labs) as well as developing dedicated funding pathways to ensure access to diagnostics.** This can be facilitated through sharing best practices on how to fund different types of diagnostics and ensure high levels of access. Both centralised funding and a tariff-based approach have a role. The funding model must take into account the need for investment in infrastructure, as well as the need to encourage competition between diagnostic providers, and it must also be sustainable over the long term.
4. There is currently a lack of information on testing methods and a lack of clear data on diagnostic uptake, as well as poor oversight of the performance of labs. **Collecting data to track access to diagnostics (and making this public) as well as putting a greater emphasis on External Quality Assessments (EQA) of labs will help to ensure consistent testing quality throughout Europe and allow comparison between approaches.** This means promoting international platforms for EQA of labs and research into quality (e.g. IQN Path) to improve diagnostics testing and make EQA participation mandatory for labs across the EU. This should also promote consequences for poor performance of labs, e.g. report to a supervisory authority.
5. Tackling delays to reimbursement of new treatments will ensure more systematic and equitable access. **This can be improved by supporting better alignment of data requirements between regulators and health technology assessment (HTA) bodies to improve evidence development and facilitate the value assessment process.** Sharing best practices on HTA methodology for PM will contribute to finding a balance between the need for an integrated approach to assess the cost of diagnostics and medicines, and the need for a more flexible approach that incorporates new technologies (e.g. NGS). This should take into account the value of personalisation in their methodologies and should be pragmatic in using the available

evidence. Interim/early access programmes can allow for early provision of innovative medicines while additional value assessment and pricing negotiations are being conducted.

Appendix: Access timelines

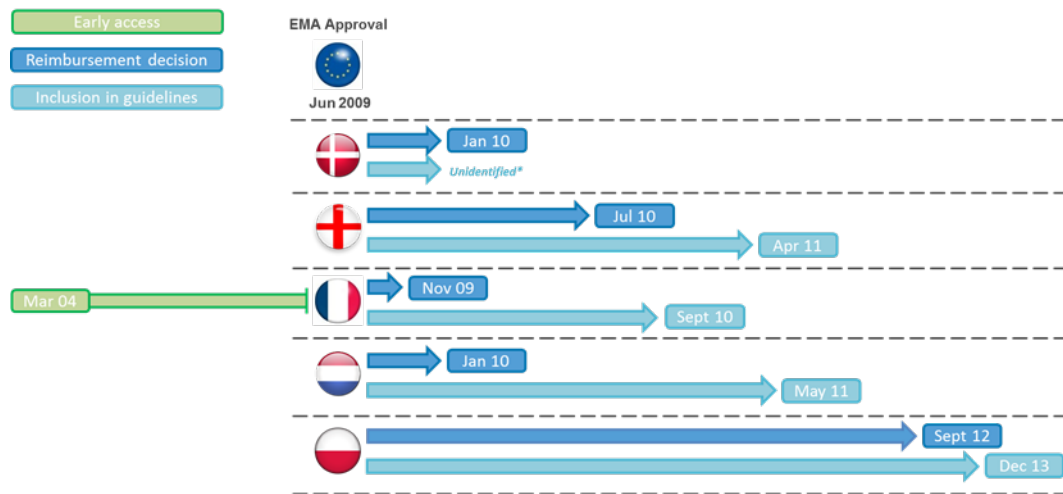
NSCLC

Considering the first-in-class EGFR and ALK inhibitors for NSCLC, France has the fastest access to novel targeted treatments (Figure 15 and Figure 16). This has been largely facilitated by the French ATU system; Iressa was first made available via a nominative ATU 5 years prior to receiving marketing authorisation by the EMA. In the past decade almost half of targeted therapies were available through a cohort ATU, granted on average 160 days before the MA.²¹⁷ Similarly, Denmark has been seen as a receptive market for targeted therapies, with early national cancer plans acknowledging the contribution of targeted cancer drugs.²¹⁸ In NSCLC, Denmark has a nationwide strategy to address lung cancer through the Danish Lung Cancer Group and was the first European country to implement a Lung Cancer pathway.^{219,220}

In contrast, treatments for NSCLC in England have faced numerous challenges to meeting required cost-effectiveness thresholds in order to achieve positive NICE recommendations. All recently approved innovative medicines required some form of patient access scheme to reduce the cost of medicines to within accepted thresholds. Negotiation of these has often led to delays in access due to suboptimal processes. In Poland, access to PM in NSCLC has been delayed and underfunded in comparison to other European markets, with reimbursement taking three years for Iressa and five years for Xalkori.²²¹ By 2017 the availability of innovative personalised treatments and appropriate diagnostics for the EGFR inhibitors and ALK inhibitors had improved. Currently all EGFR inhibitors are reimbursed, though many with restrictions, and only Xalkori for ALK+ tumours (Table 13). Xalkori only achieved reimbursement by late 2017 after multiple reviews by the AOTMiT, and after expanded use into the ROS1+ NSCLC indication.²²²⁻²²³ The national guidelines establish the access and associated restrictions for each product, with detailed clinical criteria for use of each product in specific lines of therapy and patient characteristics.²²⁴

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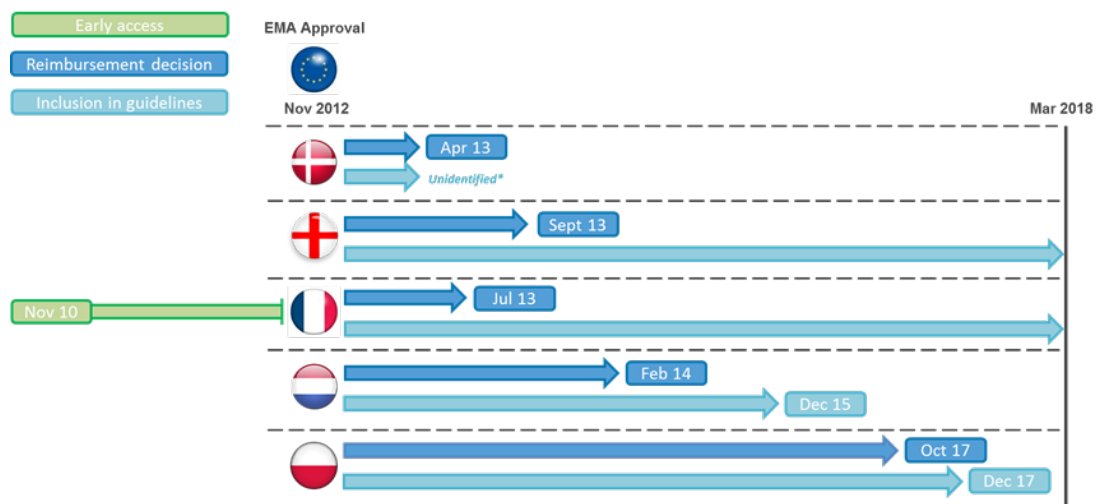
Figure 15: Iressa (gefitinib) access and uptake timeline for EGFR+ NSCLC



Notes: * Date of first inclusion in guidelines unidentified in Denmark, latest NSCLC guidelines published in 2015

Source: CRA analysis of national reimbursement recommendations and treatment guidelines

Figure 16: Xalkori (crizotinib) access and uptake timeline for ALK+ NSCLC



Notes: * Date of first inclusion in guidelines unidentified in Denmark, latest NSCLC guidelines published in 2015

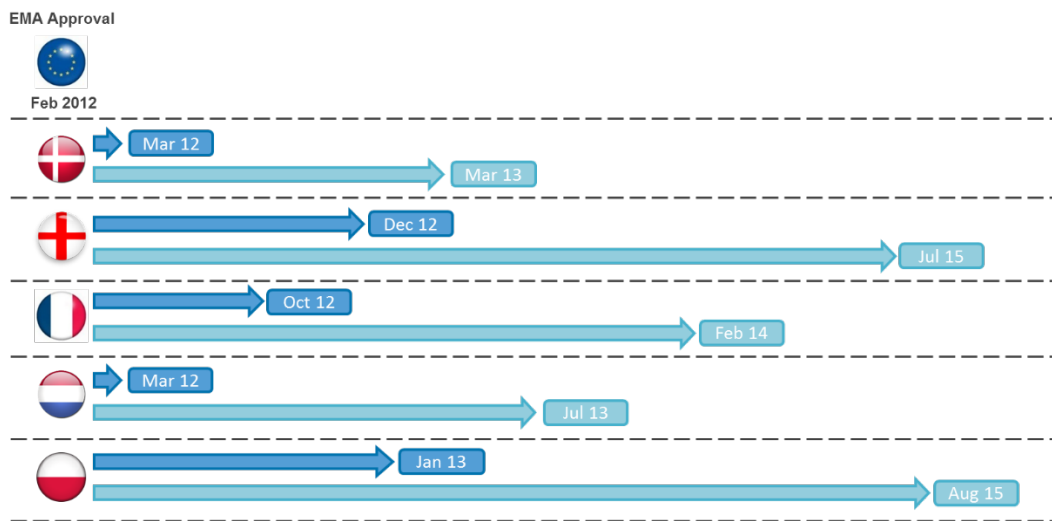
Source: CRA analysis of national reimbursement recommendations and treatment guidelines

Melanoma

In melanoma, patients in Denmark and the Netherlands have had faster access to targeted therapies, whereas in France, England and Poland this has been significantly slower, occurring six months to a year after EMA approval (Figure 17 and Figure 18). In England, however, more recently launched targeted therapies have benefited from the introduction of the Early Access to Medicines Scheme (EAMS), launched in 2014. The use of Keytruda in melanoma was the first product to be launched through EAMS,

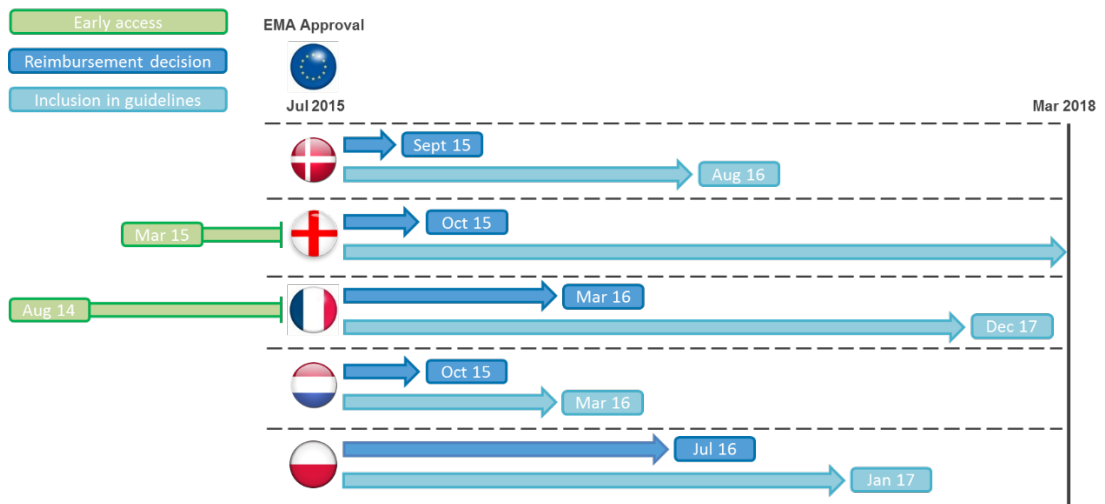
providing over 500 UK patients with early access.²²⁵ NICE has committed to start the HTA process in parallel with the MA review; earlier NICE assessment of EAMS-approved products is expected to shorten the patient access gap between EMA approval and reimbursement.²²⁶ Achieving earlier HTA requires both the company and the HTA body to engage in earlier discussions. This is already occurring in some instances; for melanoma, pharmaceutical company Merck Sharp and Dohme (MSD) was able to receive draft NICE guidance for Keytruda within five weeks of EMA approval. Timely updating of guidelines remains a challenge, however. NICE has yet to update melanoma treatment guidelines to reflect Keytruda.

Figure 17: Zelboraf (vemurafenib) access and uptake timeline for BRAF+ melanoma



Source: CRA analysis of national reimbursement recommendations and treatment guidelines

Figure 18: Keytruda (pembrolizumab) access and uptake timeline for PD-1 melanoma



Source: CRA analysis of national reimbursement recommendations and treatment guidelines

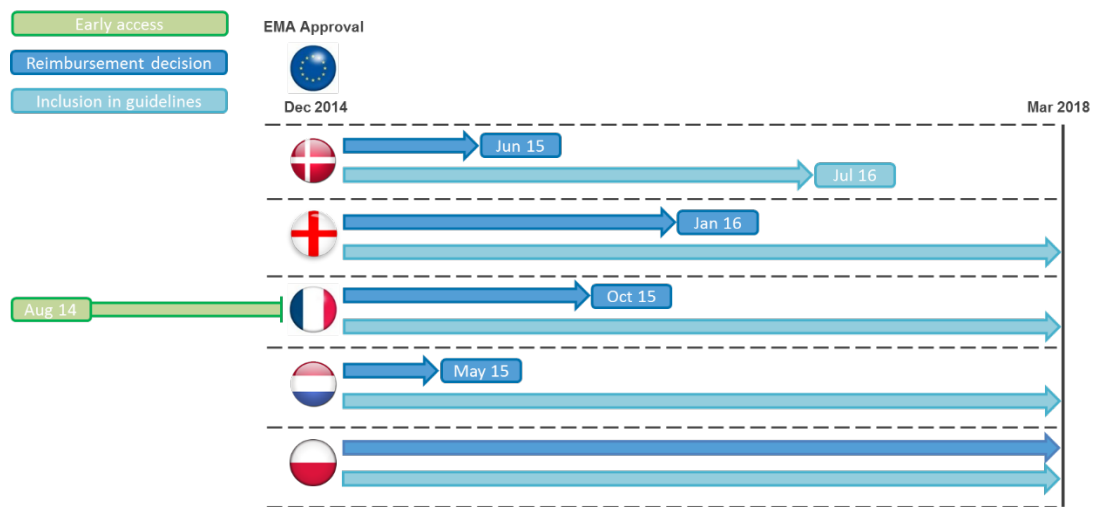
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UK Government, 23 December 2015. Over 500 UK patients gain early access to new melanoma treatment
PWC (2016). The Early Access to Medicines Scheme (EAMS): An independent review

Ovarian Cancer

In ovarian cancer, first-in-class PARP inhibitor Lynparza has seen variable access across Europe. While access has been swift in Denmark and the Netherlands, NICE only backed use of Lynparza following a reduction in prices and commitments for further evidence provision, but only after legal action from the manufacturer and in a more restricted patient population.²²⁷ NICE also set the condition that the manufacturer has to provide the drug free of charge if treatment extends beyond 15 months. Lynparza is currently not reimbursed in Poland. Inclusion in treatment guidelines has been delayed across all countries, with only Denmark updated.

Figure 19: Lynparza (olaparib) access and uptake timeline for ovarian cancer



Source: CRA analysis of national reimbursement recommendations and treatment guidelines

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Taylor, Phil. 11 December 2015. NICE changes stance on AZ's Lynparza after concessions, http://www.pmlive.com/pharma_news/nice_changes_stance_on_azs_lynparza_after_concessions_885253