THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

Access to Personalised Oncology in Europe

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ABBREVIATIONS

AA	Accelerated Assessment
ALL	Acute Lymphoblastic Leukaemia
AMNOG	Act on the Reform of the market for Medicinal Products (Germany)
AOTMiT	Agency for Health Technology Assessment and Tariff System (Poland)
ATMP	Advanced Therapy Medicinal Products
ATU	Autorisation Temporaire d'Utilisation (France)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Germany)
BiTE	Bi-Specific T-Cell Engager
BRCA1	Breast Cancer Susceptibility Type 1 Gene
BRCA2	Breast Cancer Susceptibility Type 2 Gene
CAR-T	Chimeric Antigen Receptor T-Cell
CDDF	Cancer Drug Development Forum
CDF	Cancer Drugs Fund
CDx	Companion Diagnostic
CEPS	Comité Economique des Produits de Santé (France)
CHMP	Committee for Medicinal Products for Human Use
CMA	Conditional Marketing Authorisations
CML	Chronic Myeloid Leukaemia
CPD	Continued Professional Development
DGHO	German Society for Haematology and Clinical Oncology
DRG	Diagnostic-Related Group
DRUP	Drug Rediscovery Protocol
EAMS	Early Access to Medicines Scheme
EAPM	European Alliance for Personalised Medicine
EBM	German Uniform Evaluation Standard
ECPC	European Cancer Patient Coalition
ECPDC	European Cancer Patient Digital Centre
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EOP	EFPIA Oncology Platform
ER	Estrogen Receptor
ESMO	European Society of Clinical Oncology
FDA	U.S. Food and Drug Administration
G-BA	Federal Joint Committee (Gemeinsamer Bundesausschuss - Germany)
GDP	Gross Domestic Product
GDPR	European General Data Protection Regulation
GMS	Genomic Medicine Sweden
HAS	French National Authority for Health (Haute Autorité de Santé)
HER2	Human Epidermal Growth Factor Receptor
HTA	Health Technology Assessment
IASLC	International Association for the Study of Lung Cancer

ICER	Incremental Cost-Effectiveness Ratio
INCa	National Institute of Cancer (France)
ISPOR	International Society for Pharmacoeconomics and Outcomes
LYS	Life Years Saved
MAPP	EMA Medicines Adaptive Pathways to Patients Pilots
MEA	Managed Entry Agreement
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
MoH	Ministry of Health
MSI-H	Microsatellite Instability-High
NFZ	National Health Fund (Narodowy Fundusz Zdrowia - Poland)
NGS	Next Generation Sequencing
NICE	National Institute for Health and Care Excellence (England)
NSCLC	Non-Small Cell Lung Cancer
NT	New Therapies Council (Sweden)
NUB	Neue Untersuchungs-und Behandlungsmethoden (Germany)
OECD	Organisation for Economic Co-operation and Development
OPS	Operation and Procedure Classification System (Germany)
OS	Overall Survival
PFS	Progression Free Survival
PM	Personalised Medicine
PO	Personalised Oncology
PPP	Purchasing Power Parity
PRIME	EMA's Priority Medicines Scheme
PrO	Precision Oncology Medicine
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trials
RIHN	Referentiel des Actes Innovants hors Nomenclatures (France)
RR	Response Rate
RWE	Real World Evidence
RWD	Real World Data
SHI	Statutory Health Insurance
SMC	Scottish Medicines Consortium
TLV	Dental and Pharmaceutical Benefits Agency (Sweden)
WGS	Whole Genome Sequencing
WHO	World Health Organization

EXECUTIVE SUMMARY

Background

The development of personalised oncology care, where the right cancer treatment is given to the right person at the right time determined by the use of biomarkers (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), is predicted to lead to better outcomes and reduced risk of side effects for patients with cancer as well as reducing costs and improving efficiencies for healthcare systems. The European Federation of Pharmaceutical Industries and Associations (EFPIA) asked the Medical Technology Research Group at LSE Health to conduct an evidence-based analysis to determine the use of personalised oncology medicines across Europe and to highlight barriers affecting patient access. The ultimate aim is for evidence highlighted in the report to be used to initiate discussions with policy-makers to work towards adapting and implementing personalised oncology in Europe to improve cancer-based health outcomes across the region. We refer to personalised oncology care (PO) and precision oncology medicines (PrO) in the report.

Challenges Associated with Personalised Oncology

A number of challenges associated with personalised oncology uptake across Europe were identified via a combination of primary and secondary evidence analysis. These challenges span three separate but interrelated areas:

1. Effective evidence generation

Generating evidence around the effectiveness of PrO medicines, either during development, at the marketing authorisation stage or at the HTA/pricing and reimbursement stage, can lead to multiple challenges. The main difficulties are operational and recruitment related. The fact that for some cancer types the biomarker or primary endpoint occurs in only a very small proportion of any given population means that large-scale randomised controlled trials, often seen as the 'gold standard', are difficult and not necessary. Furthermore, most clinical trials involving PrO enrol patients who have exhausted all other treatment options posing medical, clinical, methodological and ethical challenges.

The development of novel, adaptive trial processes, such as umbrella or basket trials, can deal with the specifics of PrO. As the trials enrol patients based on the presence or absence of specific biomarkers, similar patient populations can show a more consistent and predictable response to treatment meaning that fewer patients are needed to show a statistically relevant finding. They also look at shorter term treatment outcomes which can be more time- and cost-effective for product development. Furthermore, they allow flexible personalised treatment schedules and personalised mathematical models so that clinicians can adapt to potential issues associated with fixed regimes such as slowly emerging drug resistance. As a result of these benefits the number of trials with these innovative designs has more than tripled since 2010.

In addition to adaptive trial design, real world evidence (RWE) can play a fundamental role in the development and use of PrO. This data, generated under real-life conditions and using observational data including patient-reported outcomes, can supplement gaps seen in randomized clinical trials, reduce clinical and health economic uncertainty and work towards identifying better biomarkers. Utilising adaptive trials based on or complemented by RWE may reduce the time it takes PrO medicines to get to patients, provide stronger evidence of a connection between long-term impact and any surrogate endpoints, lead to a greater likelihood of reimbursement for the product in question and increase confidence in the product for both patients and healthcare providers.

2. Regulation

Current regulatory rules around the use of PrO can affect the timings of medicine approval and a key challenge for regulators will be to reduce these timelines to reduce the gap between availability and access to innovative treatments. European countries have attempted to address these challenges via approaches such as conditional approvals and adaptive pathways and individual

European countries have launched specific schemes such as the UK's Early Access to Medicines Schemes (EAMS) and the German "Heilversuch" that provide exceptional market authorisation. These schemes support the notion of medicines that address an unmet need or provide significant benefit.

The regulation of medical devices and in vitro diagnostics has changed in recent years, both at national and intergovernmental level, to keep pace with the rapid changes and to address challenges and barriers in this field, the result of 'disruptive innovation' that characterizes personalised treatments, leading to a paradigm shift in cancer medicine. Despite these updates there is still the requirement for common regulatory guidance at the EU level to harmonise the regulation of PrO medicines and companion diagnostics and to allow for 'cross-validation' of biomarker outputs generated via different clinical trials.

3. Value determination and reimbursement

It has been shown that Health Technology Assessment (HTA) processes, as well as pricing and reimbursement policies, vary across Europe. Some countries place more emphasis on clinical outcomes and comparative clinical benefit assessment whilst others are more focused on clinical and cost effectiveness. There is also a lack of alignment between the reimbursement processes used for medicines and companion diagnostics. Essentially, the payment policies currently in place for complex diagnostic/companion tests and PrO medicines are generally considered inadequate. The bodies completing the HTA process still consider large randomised controlled trials to be the gold standard but these may be difficult to perform for PrO medicines. There is therefore a need to re-examine HTA criteria, choice, quantity and quality of clinical evidence to determine if and what needs to be adapted to ensure enhanced uptake of PrO medicines across Europe.

PO Uptake across Europe

During the first decade of the 21st Century there was an increase in the number of PrO treatments and in 2019 about half of oncology trials included biomarkers. However, there is significant variation between countries in Europe in terms of access to and uptake of PO at the patient level. For example, in 2016 it was reported that as many as 5000 patients in Europe were denied access to potentially life-saving drugs to treat BRAF-mutated metastatic melanoma. About 30% of patients in Western Europe, almost 60% of patients in Central Europe and about 90% of patients in some Eastern European countries lack access to recommended first line therapy (i.e., vemurafenib & cobimetinib, dabrafenib & trametinib). There are also discrepancies in the time it takes for patients to get access to medicines. Breast cancer patients in the Netherlands, Germany and Sweden had access to trastuzumab immediately after marketing authorisation was given, whilst those in Bulgaria and Slovakia had to wait five and ten years respectively. These delays are unacceptable and can affect the survival rates of patients in countries with reduced or delayed access to PrO.

The Benefits of personalised oncology

These fit into three categories as follows:

A) Benefits for patients

For patients, PrO medicines target subgroups most likely to respond well to the interventions in question. This move away from more traditional prescribing, where medicines that may not be optimal for the patient in question are utilised from the outset, towards a situation where optimal medicines are prescribed as early as possible, leads to better patient-related outcomes, better adherence, increases in overall survival and lower risks of side effects.

B) Socioeconomic benefits

Looking at socioeconomic benefits, the estimated cost of lost productivity in early-stage breast cancer was €602 lower for patients undergoing genetic testing prior to starting chemotherapy than those not undergoing genetic testing. The use of PrO can reduce the length of hospital stays from the average week for patients treated with chemotherapy to an average of 3-4 days for those using PrO therapies.

C) Benefits to health systems

For health systems, whilst expenses may appear higher in the short term due to the additional cost

of companion or biomarker testing, in the longer term there are savings to be made. Research in France has shown that between 2008 and 2014 €459.6 million was saved on treatment with an expenditure of just over €11 million by testing for EGFR biomarkers in over 16,000 lung cancer patients to determine who would respond to available treatments (gefitinib or erlotinib). The figure for global annual waste as a result of misdiagnosis has been calculated to be as high as $350 billion.

Conclusion and Policy Recommendations

Innovation in the personalised oncology arena has the potential to improve patient outcomes and foster patient-centred care. To facilitate this, and to maximise the potential future impact of PrO medicines, there is significant work to be done to create a favourable policy environment. We have developed a full set of suggested policy recommendations aimed at policy-makers, highlighting what is required to improve equitable access to PrO across Europe. However, the following five recommendations have been prioritized:

1. A European strategy on PO use in Europe including roadmap for change setting out basic principles and objectives for the future with enhanced levels of European harmonisation and supported by appropriate resources.
2. EU harmonisation of ethics approvals to allow the sharing of anonymised, protected patient data in a pan-European network based on appropriate informed consent procedures.
3. Incorporation of 'up-to-date' information relevant to PO in undergraduate and postgraduate courses for all healthcare professionals as well a mechanism that incorporates education and knowledge around scientific advancements relevant to PO into compulsory continued professional development (CPD) for practicing clinicians. Patient associations, advocacy groups and clinicians should work towards giving health literacy a higher priority so patients feel empowered as advocates for the integration of PO into their care.
4. All eligible patients should have access to fully reimbursed, actionable mutation (biomarker) testing built into standardised patient pathways at diagnosis and disease progression.
5. Acceptance by HTA agencies of newer trial designs (e.g., basket and umbrella trials). Additionally, the EUnetHTA model should incorporate a PO pathway specifically focused on new models for evidence generation.

1. INTRODUCTION

Causing a fifth of all disease burden in the region[1], the incidence of cancer across Europe has increased from around two million to three million cases since the end of the last decade and is projected to increase to four million over the next twenty years. Mortality is expected to reach two million by 2040, almost double that seen at the end of the twentieth century. Now, close to a quarter of all new global cases (just over four million) and 20% of deaths (just under two million) occur in Europe, despite the region comprising less than ten per cent of the world's population[2].

Alongside increases in incidence there have been significant improvements in cancer survival rates[i]. For example, 5-year survival for stage 3 and 4 melanoma increased from 5% in 2010 to 52% in 2020[3]. In Denmark, 5-year net survival for oesophageal cancer increased from 5.1% in the period 1995-1999 to 14.7% in the period 2010-2014 and in the UK 5-year net survival for colon cancer increased from 47% to 58.9% in the same period[4], the result of past advances in both diagnosis and treatment[5].

Future similar increases in survival require similar future advances. The move away from a traditional model of oncology (where treatment tends to be based purely on organ-of-origin/histology) towards an enhanced use of novel 'personalised' targeted therapy, where treatment is tailored towards the individual characteristics of patients and/or their disease, will require both the widespread implementation of molecular prognostic/predictive biomarker testing as well as the introduction of a set of principles aimed at integrating personalised medicine (PM) into EU or European cancer-related health systems. This so-called personalised oncology (PO) – giving the right cancer treatment to the right person at the right time – is predicted to lead to better outcomes and reduced risk of adverse effects for the patient at the same time as reducing costs and improving the sustainability and efficiency of healthcare systems[6–8].

Recent decades have seen remarkable scientific progress in the PO arena. As of March 2020, 66 different cancer treatments, based on 25 molecular tumour alterations, have been approved by the FDA and/or EMA[9]. Progress in the policy arena has enhanced the utilisation of PO and PM as a whole and highlighted its importance in the EU. For example, in 2015 the Making Access to Personalised Medicine a Reality for Patients conference was organised by the European Commission to address the integration of PM into EU healthcare systems[10]. This emphasised the need for the development of a patient-centred approach for the benefit of European patients. In 2016 the International Consortium for Personalised Medicine (IC PerMed), which includes 20 public and private non-profit health research funding and policymaking organisations was initiated to advance these aims [11] and in 2020, the European Commission recognised the opportunity for PM to enable doctors to better tailor therapeutic strategies for the needs of the right person at the right time[12]. Similarly, the EU Cancer Plan, launched for consultation on the 4th February 2020, aims to develop a common path to lead Europe's Beating Cancer Action Plan resulting in equality in treatment across Europe by ensuring the availability and affordability of essential medicines[13]. Furthermore, the European Commission's Mission Cancer (part of the Horizon Europe Programme) has developed 13 recommendations for bold actions, including the advancement and implementation of PM approaches for all cancer patients in Europe[14].

Despite the obvious benefits and the apparent interest that progress by the likes of the European Commission over the last five or so years suggests, barriers and challenges to the enhanced implementation of PO treatments exist. For example, issues related to access disparities, for both medicines and diagnostics, a lack of precedence for new treatment paradigms in the regulatory process and incompatible requirements, processes and rules in HTA methodology. Without concerted effort these issues could become the mainstay for PO and the associated biomarkers, limiting effective use in some countries in the EU and impacting patient outcomes.

We need to work towards improving our understanding of the current barriers and challenges in order to affect change that will allow PO to have the desired impact over the next decade. Mitigating these barriers and challenges will require the concerted collaboration of all stakeholders to improve cancer outcomes in all patients across all countries in Europe.

1.1 Aims and Objectives

This report builds on work done by organisations such as EFPIA's Oncology Platform (EOP), the European Cancer Patient Coalition (ECPC) and the Cancer Drug Development Forum (CDDF)[15] to produce a thorough analysis of the state of personalised oncology utilisation across Europe. Specifically, it aims to review the value discussion and characterise the benefit of PO, analyse factors affecting decision-making related to patients' access to innovative personalised oncology and develop a set of policy recommendations related to overcoming existing challenges and incentivising the development and adoption of PO. The ultimate aim is for evidence highlighted in the report to be used to initiate discussions with stakeholders and policy-makers focused on enhancing the use of PO to improve access to effective treatments and accurate, high quality diagnostics, and improve health outcomes across Europe.

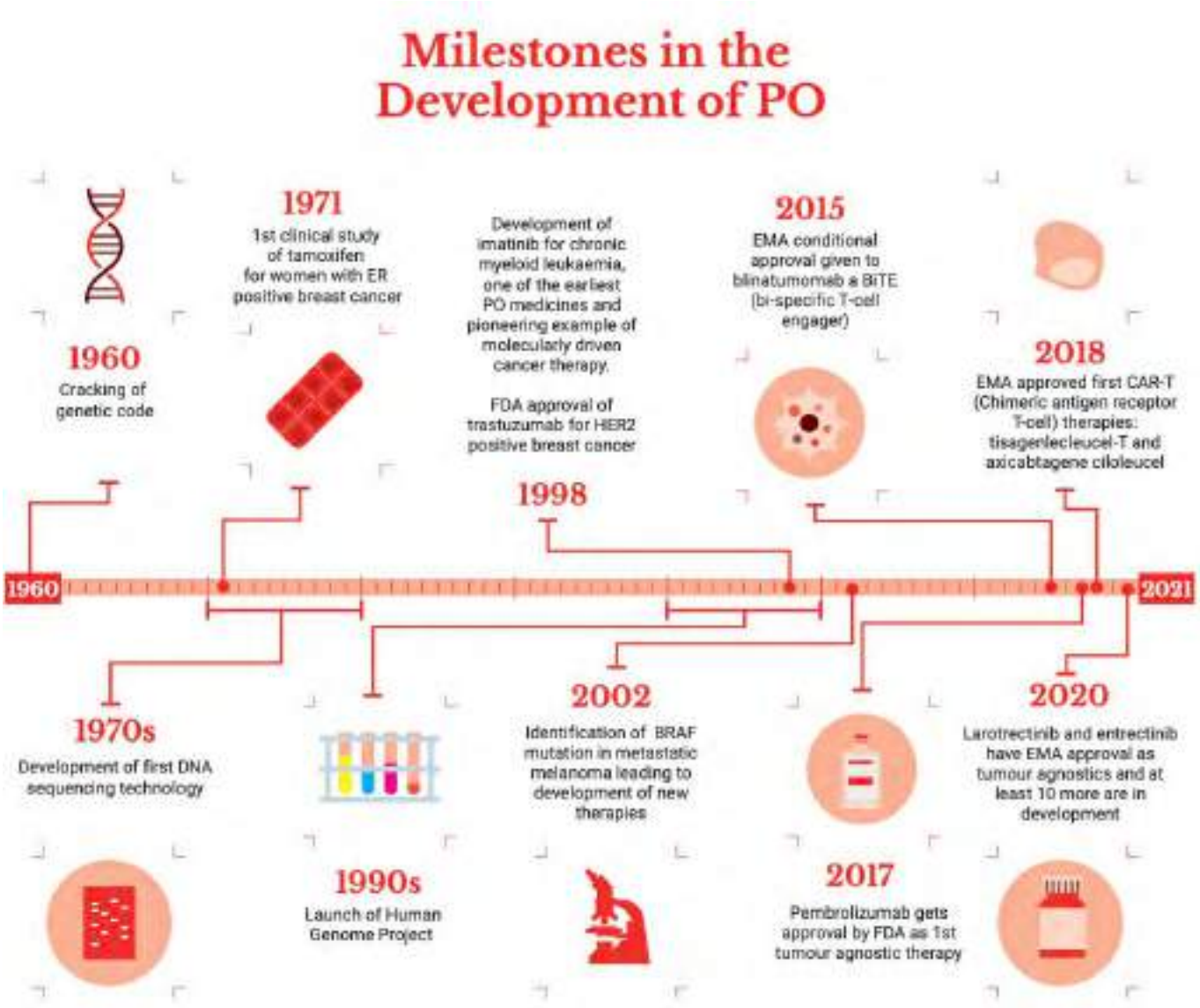
1.2 Milestones in the Development of Personalised Oncology

Before moving on to analyse the current state of PO use in Europe, and to discuss pertinent issues and challenges related to its current and future use, it is important to take some time to acknowledge the significant developments made in the field, and to understand the background to the concept of PO that we understand today.

Modern doctors have long been governed by constructs of the traditional care model – where therapies are prescribed based on population averages – but in reality, people have different ailments and symptoms as well as differing responses to treatments.

Such thoughts are exemplified by the development of tamoxifen. Prior to its discovery, breast cancer treatment tended to be on a 'trial and error' basis, focusing on surgery and standard chemotherapy for all patients. The discovery of the estrogen receptor (ER) led to the identification of the first biomarker directing breast cancer therapy (where a biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological process, disease process or biological responses to a therapeutic intervention [16,ii]). Using this molecular test physicians could pre-determine which women would benefit from endocrine therapy – women with detectable ER would and those without would not[17]. By 1971 the first clinical study of the anti-estrogen tamoxifen was carried out in women with advanced breast cancer. Its success means that it is now on the WHO list of essential medicines for the treatment of estrogen receptor-positive breast cancer in both developed and developing countries[18] and studies have shown that using it for five years significantly improves recurrence-free survival in women with early breast cancer, reducing mortality by a third 15 years after diagnosis[19].

Expansion in our understanding of genetics enabled significant progress in the treatment of cancer and the development of more personalised therapies in the late 20th and early 21st century. The 'cracking' of the genetic code (1960), development of the first DNA sequencing technology (1970s) and the launching of the Human Genome Project (1990s) were key to improving our understanding of multiple types of cancer. Numerous oncogenes and tumour suppressor genes, both implicated in tumour growth, have now been identified and progress in DNA sequencing technology (for example next generation sequencing – NGS) has allowed the full genome sequence for most common cancer types to be elucidated[20]. As early as the 1960s the connection was made between a chromosomal (genetic) abnormality and cancer when Nowell and Hungerford identified the Philadelphia chromosome, a unique genetic abnormality in chromosome 22 of chronic myeloid leukaemia (CML) cells[21]. This discovery, following further work to elucidate the genetic mechanisms of CML, led to the development of imatinib in 1998, one of the earliest examples of PO and a pioneering example of a molecularly driven cancer therapy. Its use has improved outcomes so



dramatically that estimated eight-year survival of CML increased from 6% prior to 1975 to 87% in the early 21st century[22] and it has now become a chronic disease in many cases[20].

Similar breakthroughs have improved survival rates in those with particularly aggressive forms of breast cancer. In 1979 the HER-2 gene was found to be responsible for overexpression of the HER-2 protein. The mutation, appearing in around a quarter of metastatic breast cancer cases, highlighted that HER2 overexpression could serve as both a marker of aggressive disease and a treatment target. Twenty years after this discovery the FDA approved trastuzumab (Herceptin) for the treatment of HER2 positive metastatic breast cancer, changing the outcome of one of the most lethal forms of breast cancer. The accompanying 'HercepTest', an in vitro assay which detects HER2 protein overexpression, became the first official companion diagnostic test[23].

Enhanced genomic analysis has also had a profound impact on the way in which tumours are evaluated and classified. In 2002 a mutation in the BRAF gene was identified and found to be present in around half of all metastatic melanomas leading to the overproduction and spread of cancer cells. A number of new medicines, including vemurafenib and dabrafenib, which target proteins that prevent the immune system attacking cancer cells, have been developed as a result of this discovery [24].

Between 2003 and 2013 cancer patients saw a four-fold increase in personalised treatment options. As of 2020 we are in a better position to identify the best treatment for each person with cancer based on the unique genetic profile of an

individual's tumour, regardless of where in the body it first originated. For example, the PD-L1 (programmed cell death) biomarker has been widely observed in cancers from multiple tissues of origin[25]. The PD-1 inhibitory receptor, expressed on the surface of activated T-cells, can reverse immune suppression and release T-cells. Pembrolizumab, an immune check-point inhibitor targeting the PD-1 receptor, has been approved for use in both melanoma and non-small cell lung cancer among several other tumour types[26]. In 2017 pembrolizumab became the first therapeutic to get FDA approval for a tissue/site agnostic indication[27] when it was approved for patients with unresectable or metastatic, microsatellite instability-high (MSI-H) solid tumours, signalling the beginning of a paradigm shift in the way that people with cancer are treated. Two additional tumour agnostic products - larotrectinib and entrectinib – have since been approved by the EMA. There are currently at least an additional ten tumour agnostic therapies in development[28] indicating that it is an area of intense interest and that there is unmet medical need.

Whilst not necessarily intrinsically a PO approach, unless targeted at a specific population, there has been additional progress with immuno-oncology products, where the patient's own immune system is primed to fight cancer. In 2015 the EMA gave conditional approval (in advance of full approval in 2018) to blinatumomab for patients with acute lymphoblastic leukemia (ALL). The product, a BiTE (bi-specific T-cell engager), nearly doubled overall survival compared to standard of care[29]. Similarly, in June 2018 the EMA made a landmark move for advanced therapy medicinal products (ATMPs), ground-breaking treatments based on genes, tissues or cells, when it recommended the first two CAR-T (Chimeric antigen receptor T-cell) therapies, tisagenlecleucel-T and axicabtagene ciloleucel, receive approval for B-cell acute lymphoblastic leukaemia and large B-cell lymphoma respectively. These innovative treatments were the first to be approved through the EMA's Priority Medicines (PRIME) program designed to accelerate the approval of innovative medicines, highlighting the importance of innovative PO products to Europe[30].

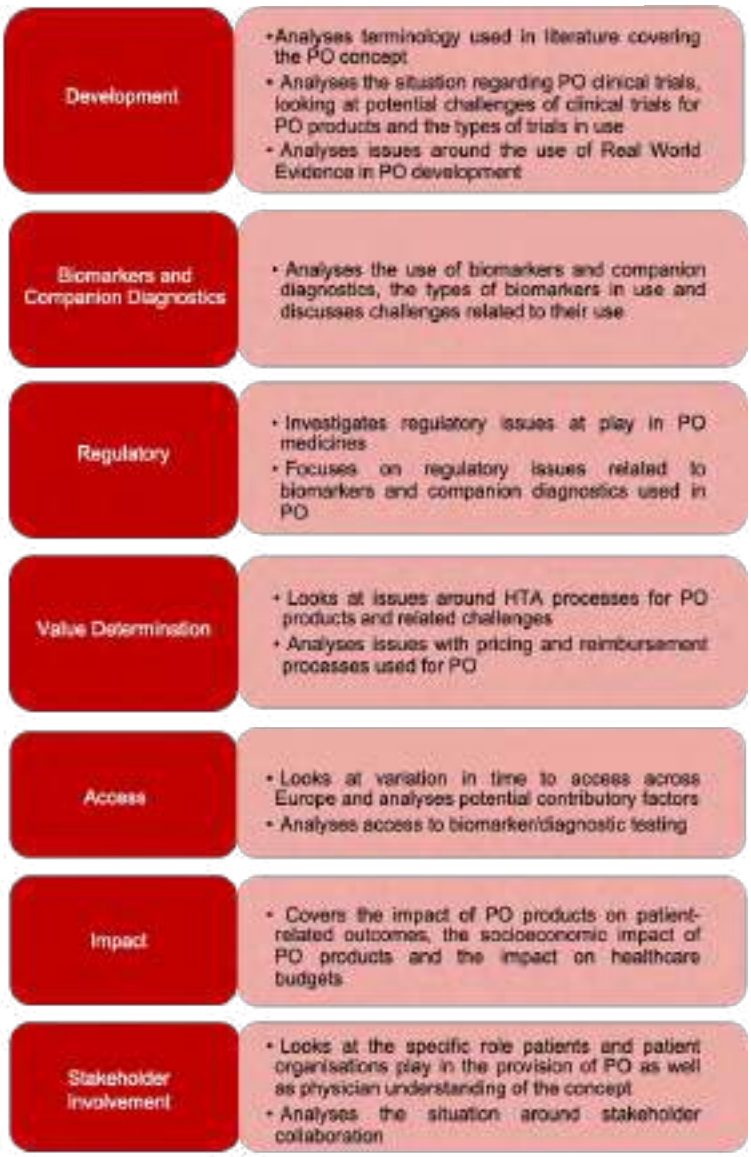
2. BRIEF METHODOLOGY

To investigate the utilisation of PO across Europe we used a combination of primary evidence, taking the form of a stakeholder interview process, and secondary evidence via a systematic literature review-based approach. The primary data collection served, among others, to create a set of five country-based case studies. Each of the areas (literature review, primary evidence and country case studies) was grounded around a set of key endpoints, forming an analytical framework, relevant to the utilisation of PO across Europe. Whilst the analytical framework is covered in Section 2.1, a full description of the methodology, including choice of country case studies, can be seen in Appendix 1

2.1 Analytical Framework

Using information from the ECPC, EFPIA, CDDF joint position paper[15], and a brief literature scan, we developed an analytical framework outlining the key issues involved in PO use in Europe. Figure 1 outlines the seven key areas within this analytical framework and explains the themes addressed in each area.

Figure 1: Analytical Framework used to guide analysis of results



METHODOLOGICAL LIMITATIONS

We were unable to include any patient representatives or patient advocacy groups during the stakeholder interview stage which may impact the resulting policy recommendations. However, we had input from ECPC throughout the drafting of this report and had their full endorsement of the final version.

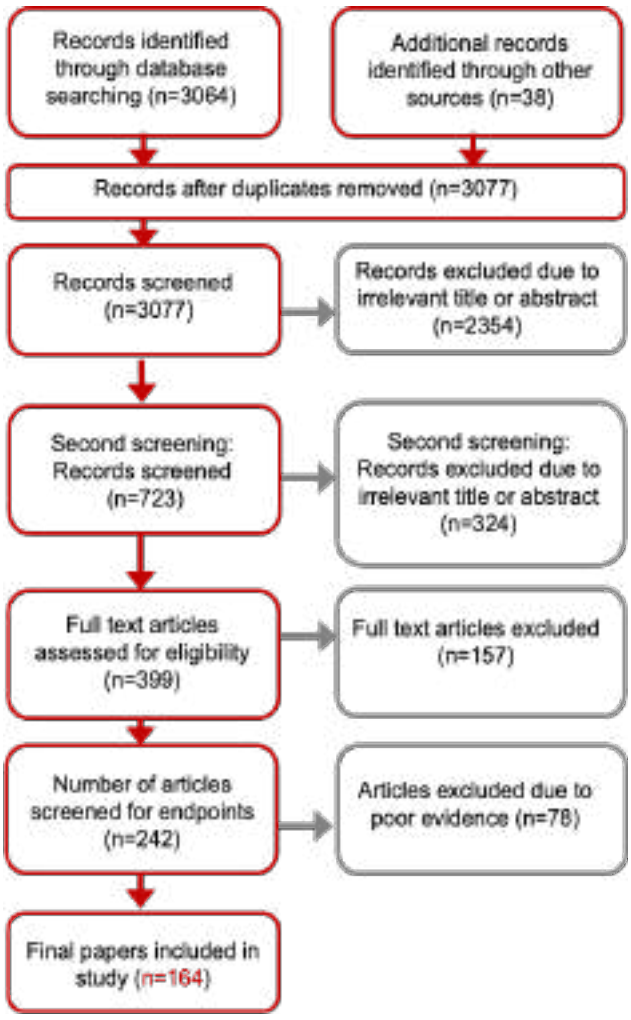
There were additional limitations related to the available secondary evidence which meant that we had to include papers between the period 2000 and 2020. Due to the fast-moving nature of the topic, there may be situations where the most up-to-date data was not available.

3. RESULTS

3.1 Literature Review

The database search yielded 3064 studies with an additional 38 studies identified from the targeted and comprehensive search for grey literature from sources including Google Scholar, WHO, ISPOR, European Commission, EFPIA, Office of Health Economics and the European Alliance for Personalised Medicine. Following removal of duplicate studies 3077 remained (See Figure 2).

Figure 2: PRISMA flow diagram with search results from the systematic literature review



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After screening for relevance of title and abstract the full texts of 242 papers were downloaded and analysed. Of these, 78 were excluded due to poor evidence related to the endpoints of interest. 164 papers were included in the literature review. Results from the targeted literature search will be discussed in Section 5 of this report.

3.2 Primary Data Collection

A total of 18 expert stakeholders were approached for interview for the collection of primary data. Between the period 24th August and 25th September 2020, we conducted semi-structured interviews with the 11 stakeholders who agreed to participate. Details of these stakeholders can be seen in Table 1. Interviews were held via Zoom where sessions were recorded as audio files. They were later transcribed, either by hand or via the Rev.com service. Themes for each country were then analysed. Results from the stakeholder interviews will be discussed alongside results from the literature review in Section 5 of this report[31].

Table 1. Stakeholder interviews conducted by LSE in five case study countries.

Country	Stakeholder Type	Organisation
England	Policy Expert/Academic	University College London
	Hospital Pharmacist	Specialist Cancer Hospital
France	Ex-Payer	Former French National Authority for Health – Transparency Commission
	Health Economist	OECD
Germany	Health Economist	Leibniz University
	Economist	Bielefeld University
Poland	Academic, Ex-Payer	Former Agency for Health Technology Assessment and Tariff System (AOTMiT)
	Clinician	Polish Coalition for Personalised Medicine
Sweden	Oncologist	Karolinska Institute
	Payer	Dental and Pharmaceutical Benefits Agency (TLV)
	Oncologist and Cancer Co-ordinator	Health and Social Care Division

4. ANALYSIS OF TERMINOLOGY

Personalised medicine as a whole has become a buzz word in both the academic and public debate around health care. The lack of clear definition means that its use is open to interpretation, complicating discussions around the associated risks, benefits and potential limits and leading to confusion on the part of patients. Having a defined, globally consistent terminology would benefit patients and their associated health literacy.

In general, three separate phrases are used to describe the concept. Personalised, stratified and precision medicine all broadly relate to similar theories and tend to be used interchangeably in different political and healthcare contexts. Our analysis suggests that the crux of the issue is the difference in meaning of the terms 'precision oncology' and 'personalised oncology'. Personalised can be seen to refer to the entire care continuum, not restricted to medicines only, where care is personalised to the needs of the person. 'Precision oncology' meanwhile refers to targeted, biomarker-driven medicines and interventions. There is therefore an argument for referring to personalised oncology care and precision oncology medicines.

Personalised tends to be the most commonly applied label in biomedical discourse when describing the future potential of molecular understanding, big-data and systems biology. In general it is the dominant term used in European political dialogue, adopted by the European Commission to denote related emerging technologies and research in the context of the European Healthcare System[32]. Here PM is defined as "*a medical model using characterisation of individuals' phenotypes and genotypes (e.g., molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention. Personalised medicine relates to the broader concept of patient-centred care, which takes into account that, in general, healthcare systems need to better respond to patient needs*"[10]. This European Commission definition places the citizen front and centre placing personal responsibility towards one's health and data.

To some the term 'personalised' reflects a potentially overambitious promise of individualised, unique medicine targeting and development so they therefore believe 'stratified medicine' '*where therapies are matched with specific patient population characteristics using clinical biomarkers*'[33] to be a more appropriate term. It has been argued that the best examples of stratified medicine are in the oncology field, with the development of cancer medicines tailored to specific molecular targets rather than clinical types of disease[33]. The word's association with racial and income stratification in the US, and ethnic and socioeconomic divisions in the UK and Europe, mean that its use has failed to gain traction in some contexts. In the US 'precision medicine' has now become the more frequent moniker and in January 2015 former U.S. President Barack Obama launched the Precision Medicine Initiative (PMI) cementing the term's use. The result is an emphasis on phrases associated with personalisation and patient centred care in Europe, and a focus on individualism, technology centred care and precision in the US.

Looking specifically at the oncology arena, a brief literature search in PubMed, analysing the number of academic articles containing the terms 'personalised oncology', 'stratified oncology' and 'precision oncology' within the body of the text published between 2006 and 2019 enabled us to investigate the evolving nomenclature-related landscape (Figure 3). In the early parts of the 21st century 'personalised oncology' is the primary term used. By 2015 the term 'precision oncology' has become the favoured term. Today this term is used in 89% of the papers analysed in 2019.

Figure 3: Publication keyword search results 2006-2019

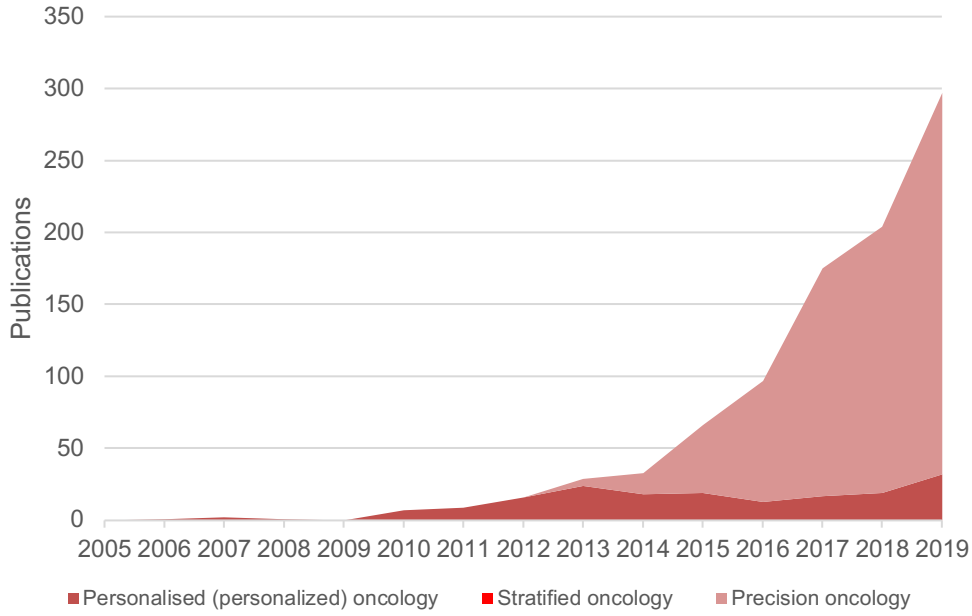
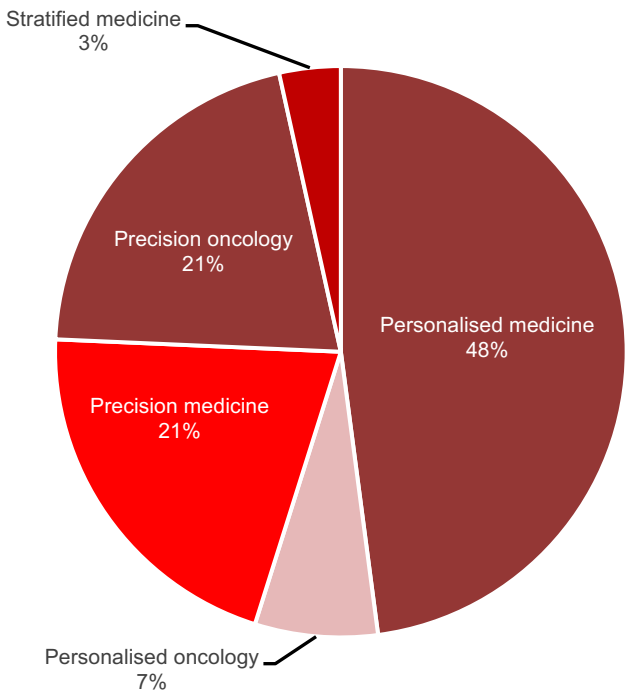


Figure 4: Analysis of terminology used in papers included in this report



Out of 164 papers included in the literature review performed for this report only 3% used the phrase 'stratified medicine' (with none using 'stratified oncology') cementing its limited use in current vernacular (Figure 4). Combined, the phrases 'precision medicine' and 'precision oncology' made up 42% of the papers included in the study, whilst 'personalised oncology' and 'personalised medicine' made up 55%. Looking purely at the 'oncology' related phrases 'personalised' was used 7% of the time, in contrast to 'precision' used 22% of the time. This suggests that when medicine as a whole is in discussion 'personalised' is more common, probably due to wider discussions around the general personalisation of medicine that has been the target of physicians since Hippocrates, whilst 'precision' is more commonly related to novel, innovative oncology medicines that require concurrent genomic investigation.

The majority of grey literature articles included in this report (from bodies like ECPC, EAPM and ISPOR) use the term 'personalised medicine'[34–40], although some also use 'precision medicine', highlighting the potentially interchangeable nature of the terminology in use[41]. Most definitions used are aligned with the broader definition which says that personalised medicine is the delivery of the right medicine to the right patient at the right time.

In the oncology setting the ESMO Personalised Medicine Task Force uses the term to describe the "*use of an individual patient's molecular information (including genomics and proteomics) to inform diagnosis, prognosis, treatment and prevention of cancer*"[41].

Stakeholders asked for their opinion on the correct working definition gave answers ranging from "*The right treatment to the right patient at the right time"* to "*Tailoring therapy to patient disease far more than previously, based on genomic make up of disease"* and all agreed the need for a common definition. One Swedish respondent made note of the difference between 'precision oncology' and 'personalised oncology', in his opinion the former being a technical term for identifying the proper patient for a specific treatment and the latter related to taking into account factors other than just the molecular target in the treatment decisions[31]. We will refer to precision oncology (PrO) medicines and personalised oncology (PO) care in the remainder of this report.

It is also important to mention the terminology involved in the diagnostic side of PO. In general, we will use the term companion diagnostic to refer to the assay of a specific biomarker which is a pre-requisite for receiving a specific PrO medicine. In Europe other validated tests can be used in place of companion diagnostics which we refer to here as complementary diagnostics.

5. ADOPTION OF PO IN EUROPE

Results from both the literature review and primary data collection were synthesised to analyse a number of issues related to the use of PO in Europe. The results are presented broadly in accordance with the analytical framework outlined in Section 2.1. The initial section covers the development of clinical evidence for PO, the use of real-world evidence (RWE) and companion diagnostics and biomarkers. Subsequent sections focus initially on regulatory pathways and potential challenges in PO in Europe before moving on to look at issues around value determination (i.e., HTA and pricing and reimbursement processes) and access to PrO medicines and companion testing in Europe. We then move on to look at benefits associated with PO from patient-related outcomes, socioeconomic and healthcare budget viewpoints. Finally, we discuss challenges related to stakeholder involvement and consider country-specific case studies before moving on to suggest a number of policy recommendations in Section 6.

5.1 Development of Precision Oncology Treatments

5.1.1 New Study Designs for Evidence Generation for PrO

The innovative and unique aspect of PrO when compared to conventional treatments means that traditional randomised controlled trials (RCT) present a set of specific challenges. The main difficulties observed are operational and revolve around feasibility, efficiency and capacity to deal with multiple small-incidence subtypes of cancer and a rapidly evolving knowledge base[42]. Challenges are encountered when there is the requirement to enrol suitable numbers of patients with relevant biomarker and genetic profiles in clinical trials[43,44]. Whilst PrO treatments might target some common mutations, they may target other, much rarer, tumour mutations. In this case a very large sample of patients needs to be screened to identify the low-frequency mutation, which is sometimes unfeasible in rarer malignancies[42,45]. Recruitment challenges might be attributed to (i) enrolment of individuals with end-stage disease, who deteriorate or die early; (ii) use of small gene panels that yield limited actionable alterations; (iii) delays in receiving and interpreting genomic results; and (iv) difficulty accessing targeted treatment drugs and/or limited drug availability[46–49].

Looking at evidence generation in general, novel studies include (i) histology independent trials which enrol patients with mutated tumours, regardless of histology, (ii) window-of-opportunity trials, when standard treatment is delayed, and patients receive first matched molecularly targeted agents allowing chemotherapy treatment-free intervals or (iii) trials that subclassify a specific disease into discrete molecular categories[50]. Specifically, in oncology, the total number of trials with innovative trial design has more than tripled since 2010[51]. Novel trial designs, which permit the testing of patients with multiple tumour histologies and/or tumour molecular aberrations are also known as master protocols[52]. Master protocols were developed in order to mitigate some of the challenges introduced by PrO therapies. These novel trials enable more efficient data collection methods due to the included multiple adaptable arms or disease histologies running in parallel[44]. Both umbrella trials, which investigate a single tumour type based on the biomarkers relevant to one or more of the treatments undergoing assessment, and basket trials, which investigate the tumour molecular characteristics and the relevant treatment-related biomarkers conducted irrespective of tumour type, fall into this category.

In comparison to conventional clinical trials such as RCTs, which usually entail large samples with high variability and reporting of average or median results, trials for PrO should involve patient stratification, which limits the population size and sample heterogeneity[35,53,54]. Smaller and targeted clinical trials for PrO help identify patients who are most likely to respond to treatments based on biomarkers[55,56]. Nevertheless, to better understand the nature of PrO therapies, we need to make sure that we use every data collection method available to aggregate information on

exponentially greater numbers of patients[44]. Traditional statistical methods used in conventional clinical trials cannot easily apply to PrO treatments[53]. The concept of personalised clinical trials introduced the idea of flexible personalised treatment schedules and personalised mathematical models, which allow clinicians to adapt to potential issues of fixed regimes such as slowly emerging drug resistance[53]. In addition, shorter-term treatment outcomes are used which appear to be time and cost-efficient in drug development[57,58].

Recent analysis by the IQVIA Institute[51] shows that the number of clinical trials incorporating pharmacogenomic and/or pharmacogenetic analysis to stratify patients for predictive response, safety, or dosing, has more than doubled since 2010 and was included in 42% of oncology trials in 2019[51].

Despite the development of novel trial methods to suit the PO paradigm, various stakeholders, including clinicians, manufacturers and researchers, face numerous challenges around these novel types of evidence generation. These trials can be time-consuming, require significant coordination among multiple stakeholders, and can be costly[52]. Due to the scarcity of eligible patients, these trials might lack a control arm and use surrogate endpoints, which might not always be well validated and their ability to predict the extent of change in more clinically relevant endpoints might not be always clear[45,59]. Furthermore, as a result of ethical considerations, most precision oncology trials enrol patients for whom standard of care options have been exhausted and they therefore may be heavily pre-treated[45]. This might decrease the likelihood of observing positive signals due to increasing lines of treatment which makes each successive treatment likely to be of less benefit[45].

5.1.2 Real World Evidence Utilisation in PO

Real world evidence (RWE) can play a fundamental role in the development and uptake of PrO treatments and should be an integral part of the development of new oncology treatments including patient-reported outcomes[34]. According to the stakeholders participating in the consultation round, RWE is the optimal way in which to maximise the benefits and the use of PrO treatments providing us with a thorough follow up on their clinical effectiveness[31]. Whilst, clinical trials are considered the gold standard of evidence generation during drug development, RWE allow for broader exploration[44]. RWE can address clinical and policy-relevant questions that cannot be answered with data derived from clinical trials[60].

Challenges due to the high levels of uncertainty surrounding PrO treatments, small patient populations and innovative clinical trial designs can be mitigated with innovative methods of evidence generation. RWE can be used to further supplement gaps in clinical trials, generating significantly more data to prove the effectiveness of a treatment under real-life conditions as well as

identifying better biomarkers that can help guide PrO therapies[61,62]. RWE can reduce clinical and health economic uncertainty by collecting further evidence on the effectiveness, safety and toxicities of PrO which can be masked in highly selected patients enrolled in RCTs for innovative therapies. This can be achieved by observing and tracking patients using conditionally approved products and supporting ongoing clinical assessment[6,7,34,63]. RWE can inform trial design, including adaptive trials, where added information about benefit can help target the right population and track clinical outcomes over time to better understand the real-world benefit of these treatments[6]. Cancer registries in particular can provide data on population-level estimates of incidence and mortality and offer insights into shifting biological causes that cannot be determined from clinical trials[60]. Evidence on disease burden, service provision and care quality can be generated by registries to inform patient care and healthcare planning as well as provide additional data for public health policy and research[34]. Use of RWE can support the development of novel therapies by exploring a wide range of information such as identifying populations who are more likely to achieve a therapeutic benefit. Genomic testing of patients can provide new opportunities for retrospective associations of tumour genomics and outcomes and contribute to predictions of disease progression, relapse, and risk stratification[64]. RWE helps to identify drivers and dynamics of routine clinical practice, evaluate therapies and associated outcomes, thereby informing the statistical design of multi-arm RCTs[64]. Data on patient symptoms and therapeutic toxicities through RWE can be valuable for clinical trial planning and design. In addition, longitudinal follow-up of patients can provide time-to-event outcomes such as time to progression and time to treatment discontinuation[64].

(A) The Requirement for RWE:

RWE refers to observational data collected from various sources such as registries, health records and non-interventional trials and can be used in the decision-making process for reimbursement of personalised treatments. It can act as a benchmarking and outcomes research process, to obtain insights into real-world cost-effectiveness of treatment pathways[7]. For instance, the first personalised treatment of melanoma in the Netherlands was reimbursed under the condition of setting up a population-based registry and centralisation of care. The Dutch Melanoma Treatment Registry was set up in July 2013 to assure the safety and quality of melanoma care in the Netherlands[7]. Other current RWE-related activities have been supported by ISPOR task force activities including indirect treatment comparisons and network meta-analyses regarding approaches to support robust comparisons across different treatments[65].

Despite the potential advantages, RWE comes with limitations. Unlike a comparative clinical trial, it cannot definitively answer the question of whether an intervention is superior to a control[63]. In addition, high quality and quantity data are needed to mitigate potential bias and lack of patient consent limits the ability to make contact with a specific patient to verify potential treatment benefits[44]. The utility of RWE may be limited when the rigor of clinical trials is needed[63]. Other methodological challenges arise with the collection of RWE due to the possibility of capturing data only from individual patient files and from pragmatic trials which are used to test the effectiveness of interventions in real-life conditions. Appropriate endpoints, comparators and statistical design should be carefully defined and selected, controlling the large risks of bias[61]. In addition, the comprehensiveness of available data is a limitation of RWE due to the lack of information regarding patient prognosis, care and outcomes, including data on performance status, disease stage, intent of treatment or disease burden, which are particularly relevant in studies of comparative effectiveness[60].

(B) Ways Forward on the use of RWE:

To maximise the potential of RWE, harmonisation in data quality and collection methods is vital to support data sharing. Data sharing can be limited due to legal, ethical, financial, and technical concerns. Usually, organisations are restricted in sharing essential data due to confidentiality agreements and legal requirements but sharing accurate molecular, pharmacologic, clinical, and treatment outcome data, particularly for rare genomic alterations and efficacy of selected therapies, will accelerate discoveries in precision

medicine research[57]. Data quality management should also be established to minimise bias[66]. Anonymising data can be impractical as traceability is required to link biomarker profiles with the disease phenotype and treatment outcomes of individual patients. Therefore, sufficient harmonisation of data protection statutes is needed to allow safe cross-border data transfer in multinational collaborations[67]. Currently, the European General Data Protection Regulation (GDPR) allows for Data Protection Boards to authorise Codes of Conduct, which might facilitate the development of more harmonised approaches[68]. A European-wide collaboration is essential to establish or extend patient registries based on harmonised, high-quality methods of data collection[34]. In addition, it is essential to secure larger sample sizes to ensure the reliability of RWE[66].

Genotype and phenotype data, including information on family history, are essential for PM and PO. Beyond registries, the use of electronic health records (EHRs) can promote electronic exchange and interoperability of patient health information, with provision of data encryption and privacy protection that can enable full interpretation of integrated genetic and genomic testing results. Emerging sources of RWE such as EHRs can offer improved granularity over traditional sources[60]. Therefore, data from EHRs can play a vital role when assessing these technologies[61,69,70].

5.2 The use of Companion Diagnostics and Biomarkers

Biomarkers in PO are increasingly used to facilitate cancer diagnosis, prognosis, treatment and epidemiology. There is a shift towards biomarker-based therapies targeting the causes of the cancer enabling us to move forward from the 'one-size-fits-all' approach [7,71,72] and improve our selection of patient populations based on the information we gain through advanced diagnostic testing. Therefore, utilisation of biomarkers can help clinicians inform treatment decisions, improve their understanding of the potential clinical benefit and toxicity of a new treatment, determine the predictive value of a treatment by identifying patients who are more likely to respond well to the treatment and further optimise the use of existing treatments by reducing the risk of adverse reactions[7,73–76]. However, the use of biomarker testing might differ across tumour types with varying adherence to testing guidelines[51]. According to the international survey performed by the International Association for the Study of Lung Cancer (IASLC), almost one-third of respondents were not aware of the most recent guidelines for molecular testing in lung cancer[77]. Variability in the use is also observed by biomarker type[51] and in oncology, universally accepted biomarkers for clinical use and clinical trials are limited[53,69].

5.2.1 Type of Biomarkers used in PO

Biomarkers fit into a number of different categories including 'predictive', 'prognostic', 'genetic/molecular' and 'surrogate' biomarkers[78]. Examples of genetic/mutation biomarkers are the epidermal growth factor receptor (EGFR) for patients with non-small cell lung cancer, the estrogen receptor (ER) protein, the Human Epidermal Growth Factor Receptor (HER2) amplification biomarker and the breast cancer susceptibility type 1 and 2 genes (BRCA1, BRCA2)[53,57,73]. Genetic endpoints are integrated at the early stages of drug development according to EMA guidance[67]. Predictive biomarkers provide information about which alterations are driving cancer growth and are used to stratify patients according to their expected response to specific treatments. They can be identified using retrospective data from large RCTs[51,53,79,80]. This type of biomarker is disease-specific, can increase the value of PrO treatments and further decrease healthcare costs[81,82].

If a certain biomarker status is a prerequisite for receiving a specific treatment, the biomarker assay is known as a companion diagnostic[75]. A diagnostic assay is used to assign participants to different candidate drugs or arms of a trial within the same trial, or a network of trials[42]. Thus, companion diagnostic tests are used to determine the molecular profile of a malignancy, in other words they are the tests for predictive biomarkers[83,84].

Prognostic biomarkers associate host and tumour variables with clinical outcomes independent of treatment, showcasing how aggressive a tumour is likely to be[85,86,80,79]. These biomarkers have an

impact on the prognosis of patients regardless of treatment, predicting the mean clinical outcome of a patient[79,85]. They can be used to stratify randomisation by disease risk, thus minimizing heterogeneity within the subgroup and maximizing heterogeneity across subgroups; to identify potential treatment targets; and to direct treatment to specific patient subgroups[79].

5.2.2 Biomarker Utilisation in Clinical Trials

New clinical trial designs (see Section 5.1.1), which allow for more efficient testing of biomarker-driven hypotheses and the biomarker-based diagnostics used in these trials, can increase the chances of regulatory approval, assign patients to treatments based on individualised factors and ultimately enhance prescribing[71,87,7]. As clinical trials for PrO enrol patients based on the presence or absence of specific biomarkers, homogenous patient populations can show a more consistent and predictable response to treatment. Thus, fewer patients are needed for the detection of a statistically relevant finding[88]. Various studies have shown that when biomarkers are used as a selection strategy in clinical trials, this can lead to more effective results[7,89]. According to one stakeholder from the industry, panitumumab used to treat metastatic colorectal cancer, was initially approved by the FDA showcasing a response rate of 10% without the use of a biomarker. When KRAS mediated resistance was discovered and added as a biomarker, response rate doubled to 20%. Taking into consideration KRAS mutation and the improved response rate, EMA approved panitumumab in Europe.

5.3 Regulatory Processes for PrO in Europe

For PrO products there are a number of existing expedited or non-traditional EU drug regulatory pathways in place to address the concepts of high unmet need, therapeutic innovation and significant clinical benefit. For instance, conditional marketing authorisations (CMA) were established to allow 'immediate availability on the market' in situations where further evidence is required. CMA, or approval under exceptional circumstances, are non-standard pathways that accept dossiers containing 'less comprehensive data' (e.g., smaller data sets, single arm trials) compared to standard or full approval. Additionally, enhanced interaction with regulators is offered via the EMA's priority medicines (PRIME) designation, a voluntary scheme based on early dialogue with developers of promising medicines to optimise development plans and speed up evaluation. Accelerated assessment (AA) allows a reduced review timeline for medicines that are expected to be of major public health interest, particular from a therapeutic innovation point of view. Eligibility to CMA, PRIME or AA is subject to review by the EMA's Committee for Medicinal Products for Human Use (CHMP) and builds on similar designation criteria. Moreover, EMA introduced the 'adaptive pathways' approach, a scientific concept for medicine development and data generation which allows for early and progressive patient access to a medicine. It is specifically designed for treatments in areas of high medical need where it is difficult to collect data via traditional routes. Whilst these pathways have been developed to address significant unmet need they are however not linked to an assessment of what is an acceptable valid condition.

As far as diagnostics are concerned, the regulations related to both medical devices and in vitro diagnostics have changed in recent years, both at national and intergovernmental level, to keep pace with the rapid changes and to address challenges and barriers in this field, the result of 'disruptive innovation' that characterizes personalised treatments, leading to a paradigm shift in cancer medicine[90]. As discussed in the previous section, there is a resulting impact on evidence generation, changing how oncology trial designs are shaped and conducted[91]. While there are few stand-alone national plans or special regulations focused specifically on PO in European countries, PO is the object of interest for national health authorities in most countries[31]. At the EU level the EMA has recently updated its regulatory framework to address issues on transparency in relation to quality, safety and cooperation between relevant stakeholders. The regulatory framework in Europe moved from three directives (Directive 90/385/EEC, active implantable medical devices; 93/42/EEC, medical devices; and 98/79/EC on in-vitro diagnostics)[92] to a comprehensive reform of medical devices legislation in April 2017, with the

adoption of two regulations: Regulation (EU)2017/745 on Medical Devices[93] (Official Journal of the European Union, L117/1) and Regulation (EU) 2017/746 on In-Vitro Diagnostic Devices[94] (Official Journal of the European Union, L117/176). These new regulations among other things expanded the required information for submission and for post-market surveillance, reclassified devices according to risk and required more rigorous clinical evidence to enhance safety and efficacy. The new in vitro diagnostic regulation also requires laboratory-developed tests to obtain CE-IVD marking (Official Journal of the European Union, L117/176), regardless of where they are developed. This is in contrast to the previous regulation which allowed for automatic exemption for laboratory diagnostic tests. As a result, single healthcare institutions will be required to meet all relevant requirements for safety and performance, providing a justification for not manufacturing under an appropriate quality management system and making publicly available certain details of the complementary laboratory diagnostic test.

Overall, three main challenges around the regulation of PO products are summarised below[65,75,90,95,96,97].

5.3.1 Companion Diagnostics and Limited Regulatory Incentives

Europe follows different processes for the marketing approval of medicinal products and companion diagnostics[38,55,84,98]. Furthermore, in order for a pharmaceutical product to receive a marketing authorisation there is no requirement for the submission of specific companion diagnostic tests. This can lead to the adoption of a diverse range of tests that are consistent with the marketing authorisation[83]. However, the presence of a companion medical devices/test can allow pharmaceutical companies to frame a 'stronger argument' to regulators and insurers on both the cost-effectiveness and clinical outcomes of the PrO medicine via stratification of the population. For example, gefitinib regained marketing authorisation in Europe by submitting the EGFR mutation test after a previous withdrawal due to failure to prove survival benefit in phase III trials[83].

The adoption of companion diagnostics can also have retrospective implications. In fact, a review of FDA approved drug labels reported that, from 1945 to 2005, approximately 10% (121 out of 1200) of labels included useful data for a potential personalised treatment based on a genetic test[99]. By 2019, 70 oncology products required or recommended predictive biomarker testing[100]. Looking at Europe, in 2019, nine new oncology treatments were approved by the EMA, five of which were associated with a predictive biomarker and two had an approved companion diagnostic[51]. Furthermore, between 1995 and 2014, almost 15% of EMA-evaluated medicines contained pharmacogenomic information in their label[101].

Some commercial gene expression prognostic tests, such as MammaPrint (Agendia) and OncotypeDX (Genomic Health), have proved to be successful, but there remains regulatory and reimbursement uncertainty around the clinical validity and expected utility evidence of such tests[96]. The two new regulations focused on medical devices and in-vitro diagnostic devices discussed in the previous section demonstrate that both the EU and EMA are striving to keep pace with the advancement of diagnostics and their use for PrO therapies, however the scenario is constantly evolving, and further efforts will be required to enhance regulation (see Section 6).

Overall, there are still challenges in companion diagnostics regulation that need to be addressed. In the European regulation issued in 2017 the review of companion diagnostics is primarily based on notified bodies, which are currently restricted in terms of providing advice and consultation to industry. Additionally, scientific advice for developers is not guaranteed[98]. Significant resources are needed to discover biomarkers, develop assays for biomarkers, and develop a diagnostic assay which can meet regulatory requirements for parallel approval with the PrO medicine as a means of selecting suitable patients [81]. In order to be able to maximise the potential of PrO medicines linked to biomarkers, it is essential to ensure optimal adoption of biomarker testing[51].

There is no agreement and no common European consensus on the criteria or level of clinical utility, quality assurance, nor on the assay validation, including analytical and performance requirements, reproducibly, robustness and laboratory accreditation, required for different types of biomarker assay, and the selection criteria for

appropriate laboratories to perform clinical trials[61,102]. A common guidance at EU level is needed to harmonise standard operating procedures for biomarker assays and to cross-validate biomarker outputs generated from different clinical trials[61]. In addition, the new European regulation, in contrast to the US FDA, does not define companion diagnostics as useful for 'monitoring treatment with a medicinal product for the purpose of adjusting e.g., dose'. This omission in the definition could restrict the use and reimbursement of companion diagnostics[103]. There is an unmet need to improve the systems in place for developing relevant biomarker tests or specific genetic characteristics available in parallel with PrO treatments in order to avoid a situation where patients do not receive optimal treatments, potentially resulting in diminished patient outcomes and reduced survival[51,62]. As a first step, in order to promote harmonisation and standardisation of genetic testing services, the European Union has created the EUROGENTEST2. This project has the goal of coordinating genetic services and sets benchmarks for laboratory and health professional accreditation and diagnostic validation as well as benchmarks for quality management and training activities[104].

5.3.2 Issues with Review Timelines

The regulatory rules around the use of PO can affect the timings of medicine approval and a key challenge for regulators will be to reduce these timelines[1,7,105]. Currently, there is a gap between availability and access of innovative treatments. Review procedures to determine that an innovative treatment is cost-effective are often lengthy and replicated at different levels of government[34]. In a recent publication EFPIA outlined three categories of delays in access to oncology medicines: (a) process, i.e., how stakeholders organize the series of steps to take; (b) reimbursement criteria, i.e., what information stakeholders use to define value; and (c) health system readiness, i.e., to what extent stakeholders integrate the therapy in clinical practice[106].

Adaptive design trials can reduce clinical development timings, as well as facilitating dose selection, reducing the number of patients exposed to ineffective doses, improving calculation of samples size and reducing overall costs[58]. Clinical trials with adaptive characteristics are recognized by both the EMA and FDA as viable alternative strategies for both early and pivotal trials in the regulatory environment. However, regulatory agencies still seem reluctant in some cases to approve adaptive designs due to potential difficulties interpreting results[58]. Shorter trials may be less able to capture substantial differences between new and existing products, leading to a greater uncertainty compared with longer, traditional clinical trials[107]. However, the advantages of adaptive trials based on RWE may include: a reduced time to market access; stronger correlation between long-term impact and surrogate endpoints; greater likelihood of reimbursement; and an increased confidence in the product by providers and patients[107]. An adaptive and iterative approach could allow early revenues for manufacturers and to assess clinical efficacy and safety both during exploratory trials and while the product is on the market. From 2014 to 2017 EMA received 78 requests for accelerated appraisals, of which 50 were accepted, with a peak of 17 approvals in 2015[107].

Companion diagnostics and medicines have two separate review and approval process timelines [98] and these varying timelines could represent an issue if they result in delays in the medicine review or approval. While European pharmaceutical legislation provides accelerated approval pathways, the in vitro diagnostics regulation does not consider them[98]. Overall there is a lack of coordination between companion diagnostics and medicines review processes that could cause time lags, especially if a medicine has been approved via an accelerated pathway[98].

European countries have attempted to address the new challenges related to the length of the market authorisation process brought about by new medicines and new sources of evidence. As discussed earlier, approaches like conditional approvals and adaptive pathways pilots (such as the EMA Medicines Adaptive Pathways to Patients pilots (MAPPs) and priority medicines scheme (PRIME)) are available within the current regulatory framework[108,109]. However, these initiatives have not been widely utilised as there are criticisms and uncertainties in the effectiveness of new treatments. All new treatments that were considered in the USA for accelerated approval

between 2009 and 2014 were assessed with intermediate endpoints, which are accepted in Europe only on an exceptional basis. These uncertainties cause delays at national and regional reimbursement decision levels, since EMA assesses quality, safety and efficacy only[110]. Furthermore, individual European countries have launched specific schemes such as the UK's Early Access to Medicines Schemes and the German 'Heilversuch' that provides exceptional market authorisation[111]. At the EU level, MAPPs allow an early authorisation for a targeted subgroup of the population with a specific safety and efficacy profile. However, this scenario is considered transitional as many stakeholders suspect that adaptive pathway approvals could become the rule rather than an expectation[111]. A final challenge for adaptive pathways relates to the shift from pre-marketing to post-marketing evidence. Issues such as early patient access, public health right and societal benefits could be seen to be competing and it will remain a challenge for regulators to ensure timely approvals whilst at the same time ensuring the quality of the evidence and fair competition[111].

5.3.3 Lack of Regulatory Harmonisation across Countries

The new EU regulations issued in 2017 [94] attempted to address issues around transparency, safety and efficacy of the market authorisation process but there is still room to enhance regulatory harmonisation across European countries. With regards to the PO related constituent components, there is still a lack of aligned processes from a regulatory approval standpoint that may cause uncertainty in the potential for return on investment[65]. The advent of NGS will drive regulators to change regulatory approval for PrO medicines and to modernise approval mechanisms in light of new evidence sources and recent developments by clarifying areas of uncertainty and moving towards standardised regulatory and reimbursement practices.

Furthermore, trials have to adapt to different regulatory testing requirements across countries within Europe. In the future, using similar platforms and criteria across countries would help with development[90]. Currently there is a lack of a general regulatory framework for different commercial biomarkers analysing detailed biological characteristics that may be relevant for a specific class of targeted drug, generating potential confusion in daily clinical practice[75]. Relevant stakeholders could be involved to establish a developmental framework that would improve assay performance prior to regulatory approval[75]. Key European stakeholders generally agree that greater collaboration across involved actors (regulatory agencies, pharmaceutical and biotechnology companies, patients and physicians organisations among others) and harmonisation between countries at the EU level may lead to improvement in European regulation as practices in clinical development and evidence generation, as well as the audit process between regulators and pharmaceutical and biotechnology companies, can be further enhanced[31].

5.4 Value Determination of PrO Treatments

5.4.1 HTA Systems and the Value of Personalised Oncology

Criteria underpinning the HTA process vary across countries within Europe, with some countries giving relatively more emphasis to clinical outcomes and clinical benefits, and others to cost effectiveness[31]. A consortium of European researchers (HISCREENDIAG) showed there is heterogeneity in the HTA decision-making process and specific criteria related to genetic screening for PM, as well as a lack of alignment in the use of HTA for the reimbursement of diagnostics[71]. This can have a resulting impact on value-determination processes utilised across and even within countries for different types of technologies[95,108]. There are also inconsistencies in cost-effectiveness estimates for pharmaceutical and companion diagnostic combinations across HTA markets, where improvements in economic modelling, sensitivity analyses and value assessment are needed[39]. An example is EGFR testing before the gefitinib trial, where the manufacturer determined the cost-effectiveness estimate was £23,612 per quality-adjusted-life-year (QALY), while NICE in England estimated £35,700 per QALY and SMC in Scotland

up to £154,022 per QALY[39] (if compared to pemetrexed/cisplatin, included in the first submission in Scotland)[112].

Authors analysing the value assessment criteria for PrO and companion diagnostics highlight the importance of measuring adverse effects or changes in incidence related to diagnostics and the associated therapeutics, and that immediate patient outcomes (e.g., blood pressure) and overall health outcomes (cancer survival) might not be sufficient criteria for a positive reimbursement decision[113]. Others stress the need to adopt two additional parameters to assess value, i.e., feasibility (e.g. acceptability, clinical contradictions, failure rates) and test process (e.g., procedural harms or benefits, placebo effect)[114].

Reimbursement decisions based on limited evidence are challenging for HTA bodies, which still consider large comparative RCTs the gold standard[7]. Therefore, a challenge for defining the value of PO is the provision of rigorous clinical evidence[35]. However, as discussed earlier, for some cancer types the biomarker or primary endpoint occurs in only a very small proportion of any given population. This raises concerns around how best to assess comparative treatment efficacy and patient response[115]. Similarly, outcome-based pricing contracts, such as managed entry agreements, could be used for innovative products that report high clinical uncertainties[7]. Sweden launched the 'Coverage with Evidence Development' programme, which ties reimbursement decisions to the development of additional evidence[7]. There is also the potential for HTA bodies and regulators to improve RWE data requirements (see Section 5.2) to enhance their use. As RWE collection is a relatively recent practice there is still the requirement for it to be fully and effectively integrated into the HTA process. Currently, parallel scientific advice consultations between EMA and HTA bodies are working towards addressing these gaps[7].

To summarize, value determination represents a challenge for HTA bodies and for health systems. HTA criteria, choice, quality and quantity of clinical evidence will have to be re-examined to determine if and what needs to be adapted. Most key stakeholders interviewed in this study agreed that these will be challenges that will have to be addressed to implement new personalised therapies[31]. In an attempt to develop common methodological approaches, and facilitate information exchange at the European level, the European Commission established EUnetHTA, which is an HTA network between European member states[34]. It aims to consolidate some aspects of the HTA assessment process within the EU and can be used as an initial point for both cross-country and agency collaboration[116]. EUNetHTA developed methodological guidelines on joint assessment in HTA and worked towards promoting synergies in research on this topic among EU countries[117,118]. It is a step towards a harmonised clinical HTA process which has the potential to reduce workload, create efficiencies and underpin faster patient access to life preserving treatments[119]. However, EUnetHTA activities will end in 2021.

5.4.2 Pricing and Reimbursement Decisions

As with HTA-related value determination, pricing and reimbursement policies differ across countries within Europe[95] and there is a lack of synchronisation between the reimbursement processes in place for medicines and companion diagnostics[120]. Pharmaceutical companies face increasing challenges in balancing market access and pricing for PrO products in Europe due to the fact that, in recent years, most European countries have adopted different pricing and reimbursement policies, such as price cuts, international reference pricing, generic substitution, managed entry agreements, rebates and clawbacks, budget caps, tendering and selective contracting[107].

Companion diagnostic funding can be provided by the health system, pharmaceutical companies and, in theory, paid directly out of pocket by the patient, who in most cases are then reimbursed by the health systems[38]. Health systems can reimburse companion diagnostic testing through the diagnostic-related group (DRG) system, the fee-based system and the budget-based system[121]. With the DRG system, a patient is assigned to a DRG which corresponds to a flat rate fee that includes pharmaceutical medicines and companion diagnostic test expenses. In the fee-schedule based system patients are reimbursed with generic or specific codes related to a given test. Finally, in budget-based systems laboratory

services are based on global annual budgets, where funding is allocated for diagnostics. Pharmaceutical companies may be forced to pay for companion diagnostic testing, for example, in order to promote the uptake of a specific product. An example is the BRAFV600 mutation test for vemurafenib which has been paid for by a pharmaceutical company in the UK[38]. In some European countries the reimbursement of clinical diagnostic tests is done at the regional or hospital level[122] (e.g., Italy and Spain), with process differences between in-patient and out-patient treatments, while coverage for prescription medicines is completed at the national level[121]. This could cause misalignments in the reimbursement process of medicines and companion diagnostics[121]. There is also variation in reimbursement across countries in Europe. For example, in the UK, Germany and Italy the HER2/neu diagnostic test required for treatment with trastuzumab is publicly funded, while in Spain it is covered by a therapeutic partner[71,108]. Such differences can have implications on patient access.

Despite an EU Directive on pricing and reimbursement of oncology medicines specifying a 180-day limit post EMA authorisation for national implementation there is significant variation in terms of compliance with this deadline[98]. For example, there were marked differences in time to approval and reimbursement experienced by trastuzumab. Germany, the Netherlands and Spain had rapid reimbursement but delays were evident in the UK, Belgium and Denmark, ranging from 500 to 1800 days. Delays in Eastern Europe were more pronounced, all broaching the 2000-day barrier[119].

A challenge then is that payers across Europe are adopting different payment and evaluation models for medicines and diagnostics[108]. Reimbursement challenges also exist due to the level of requested evidence, particularly related to diagnostic tests[31]. Key European stakeholders report that there is a lack of linkage between pre-market review of pharmacogenetic applications (which are different from biomarker tests), HTA processes and reimbursement decisions, and that evidence of pharmacogenetic tests may have to be improved[123]. Current coverage payment policies for complex diagnostic tests and PM are generally considered inadequate[96].

Different authors argue about the opportunity for changing the criteria surrounding companion diagnostic reimbursement decisions, moving from a cost-based to a value-based approach, and adapting the reimbursement criteria to be more in line with those associated with the pharmaceutical products themselves[121,124]. Some countries are embracing pay-for-performance models. An example is the Netherlands, were the Dutch Health Care Institute and insurance agencies adopted a novel reimbursement model to reimburse successful cohorts from the drug rediscovery protocol (DRUP), providing access to medicines for patients with rare tumour profiles and allowing further confirmation of clinical benefit in larger cohorts of patients[47]. The European Union is also trying to stimulate the development of infrastructures for clinical evidence and to harmonise country efforts with the EU Framework Programme for Research and Development providing €70 billion worth of resources to develop PM and related data infrastructure[67].

5.5 Access to PrO across Europe

As discussed in the previous sections, the development of, and increased access to, PrO has been an explicit goal for the European Commission as the increasing burden of cancer represents a major challenge for health systems[125]. Since 2010 the European Commission has launched a number of workshops to analyse various aspects of PO[126]. Despite the challenges discussed earlier, over the last decade regulations have been adapted to encourage uptake of and access to personalised oncology therapies. Addressing challenges related to the uptake of these new approaches is also within the scope of Europe's Beating Cancer Plan and the Mission on Cancer of Horizon Europe[14]. Two of the 13 Mission recommendations are explicitly related to PO. Goals are focused on advancing, scaling, implementing and optimising PO and creating a European Cancer Patient Digital Centre (ECPDC) where cancer patients and survivors can deposit and share their data for personalised care[127].

5.5.1 Uptake of PrO Treatments and Biomarker Testing

The uptake of PO increased in Europe over the first decade of the 21st Century. Between 2006 and 2010 the investment companies made in PM increased by a mean of 75%[128] and by 2015, specific biomarkers were used in almost 50% of the early-stage pipeline assets and in 30% of late-stage molecular entities[71]. However, there is significant variation between countries in Europe in terms of access to and uptake of PO at the patient level. For example, in 2016 it was reported that as many as 5000 patients in Europe were denied access to potentially life-saving drugs to treat BRAF-mutated metastatic melanoma. About 30% of patients in Western Europe, almost 60% of patients in Central Europe and about 90% of patients in some Eastern European countries lacked access to recommended first line therapy (BRAFi and MEKi combination – vemurafenib & cobimetinib, dabrafenib & trametinib)[129]. Furthermore, time to access can vary significantly. Patients in Bulgaria had to wait five years for access to trastuzumab, now included in the WHO list of essential cancer medicine, whilst those in Slovakia had to wait ten years. In contrast, breast cancer patients in the Netherlands, Germany and Sweden had access immediately following marketing authorisation[34]. Looking at novel oncology products in general, time from marketing authorisation to granting of coverage has been shown to vary from four months in Sweden to 27 months in Malta[59].

In general uptake of PO treatments can be hampered by three main barriers excluding regulatory challenges: a.) clinical utility of the product and any associated diagnostic; b.) the specific reimbursement process; and c.) health economics of PM versus standard of care[130]. Furthermore, there are still a number of factors that can affect uptake and patient accessibility, even after marketing authorisation approval by EMA. As discussed previously some of these factors include[7]:

- The HTA methodology applied and the mechanism of value assessment in use in the country
- The degree to which medicines are reimbursed or rejected
- The length of time it takes to complete the pricing and reimbursement process
- The role of guidelines in uptake in the country and how quickly and frequently these are updated
- Funding pathways in place for PO and allotted investment potential.

There are also visible differences within countries as coverage decisions are sometimes taken at sub-national level, causing potential inequities in access[7]. Overall a country's economic strength is correlated with access to oncology medicines as public payers are more willing or able to reimburse new medicines[1]. European countries are attempting to address the affordability issue by creating, for example, dedicated budgets for oncology such as the Cancer Drugs Fund (CDF) in England, which also aims to set a process to create access while evidence is developed. Similarly, countries have attempted to decrease time to authorisation with pathways such as France's authorisation of temporary usage (ATU).

As far as diagnostics are concerned, frequency of biomarker use both in the development of PrO treatments and in clinical practice has increased exponentially over time, enabling stratification of patients who are more likely to respond well to treatment. In 2015, specific biomarkers were used in almost 50% of the early-stage pipeline assets and in 30% of late-stage molecular entities[71]. It is expected that the companion diagnostics market will continue to grow in the future. Agreements and partnerships between pharmaceutical companies and diagnostic manufacturers increased from seven in 2008 to 25 in 2010, with the vast majority (77%) focused on oncology indications[92]. As companion diagnostics are linked to the value of PrO treatments, access to testing could be driven by the PrO treatment manufacturer[7].

In Europe, disease-specific funding covers diagnostic services as part of broader efforts to improve oncology care. This has allowed for infrastructure investment and high levels of access. In France for instance, there is good access to lab-based testing services. However, there is limited access to specific diagnostic kits. Both France and Denmark have set up national programs to support molecular testing with the establishment of regional molecular genetics centres. However, Poland was

reported to have significant gaps between demand and provision for testing in some cancers, such as lung cancer. England's approach to testing has been relatively fragmented up until now, leading to significant variation in access to diagnostics[7].

In terms of clinical trials, the clinicaltrials.gov database website reported in 2015 that there were about 100 clinical trials (Phase II, III and IV) in which diagnostic information was included as a primary or secondary outcome measure as well as inclusion/exclusion criteria for patient enrolment[131]. The IQVIA Institute[132] stated that, in 2019 about half of oncology trials included biomarkers related to the medicine's efficacy, toxicity, or pharmacogenomic patient stratification[51].

Evidence from primary stakeholders[31] suggests that the use of diagnostic tests depends on where patients are treated and who commissions the treatment. In larger and/or university hospitals in larger cities, diagnostic tests and biomarkers are more likely to be used to facilitate cancer diagnosis and treatment selection. In Germany, diagnostics are reimbursed, or are covered by hospital funds if patients receive inpatient care. In the outpatient care setting, diagnostic tests are funded through the EBM (German Uniform Evaluation Standard) catalogue[31]. In Spain, the majority of biomarker testing is not reimbursed by the government and testing is expected to be provided by pharmaceutical manufacturers. Use of biomarkers might also depend on the treatment label and whether genetic testing before the use of the treatment of interest is necessary or not. In Poland, access to both biomarker testing and related precision technologies in remote areas can be limited, particularly if the treatment is administered intravenously (and therefore within the hospital setting). Single and small gene panels tend to be used more than comprehensive genomic profiling testing in Sweden. In France, an increasing number of NGS tests are performed. Overall, stakeholders were aware of variations in the use of biomarkers testing both across and within countries. For instance, in an international survey performed by the International Association for the Study of Lung Cancer (IASLC), respondents who request tests and treat patients believe that less than half of the patients in their country currently receive molecular testing. Their views varied significantly across regions[77]. Some stakeholders were sceptical on whether the benefits of biomarkers and companion diagnostics can offset the challenges of their use. In stakeholders' opinion, cost is one of biggest challenges considered. Multiple tests and genomic profiling will always be useful for building a detailed patient profile but in many countries in Europe there remains a question around funding. Indeed, in the international survey of IASLC, responders stated that the most frequent barrier to molecular testing in all the study regions was cost[77]. In Europe, access was the second-highest ranked barrier[77].

5.6 Impact of PrO Treatments

5.6.1 Impact on Patient-Related Outcomes

PrO treatments promise improved clinical efficacy on patient outcomes in comparison to conventional treatments. Given that these treatments target patient subgroups who are more likely to respond well to these treatments, better patient-related outcomes such as improved efficacy and overall survival and reduced adverse events are recorded[7]. The introduction of PO has allowed targeting of the underlying genetic mutations in diseases, offering the opportunity to achieve initial prescription of optimal therapies and ultimately deliver better patient response[7]. Therefore, these therapies are more likely to be more effective in improving response rates, progression-free and overall survival in defined subsets of patients identified by biomarkers rather than all patients[115,133–136]. For example, panitumumab, used in colon cancer, was shown to be effective only in cases without the KRAS mutation in the tumour[137,138]. Therefore, when PrO treatments are used in suitable patient populations, identified by molecular profiling, better clinical outcomes have been observed compared to unmatched or conventional treatments or placebo[7,50,52,57,136,139–142]. For instance, a meta-analysis of phase II clinical comparing response rate (RR), progression-free survival (PFS) and overall survival (OS) in the arms of a clinical trial that used a personalised strategy versus the 'non-personalised' arms showed that PrO treatments had higher response rates in comparison to non-personalised targeted arms, which had poorer outcomes[7]. In addition, the use of genetic markers to facilitate safer and more effective dosing

regimens and the selection of patients can reduce the likelihood of adverse events[7].

Despite the fact that there is robust evidence in the literature to show that PrO treatments lead to better outcomes in key clinical endpoints, some stakeholders raised their concerns regarding substantial improvements in mortality rates or major improvements in patients' quality of life associated with targeted treatments[31]. According to some stakeholder's, improvements in patient survival has been incremental rather than transformative. While PrO treatments have modified prognosis for some cancers or those with certain mutations, cure rate has not increased substantially[133]. However, according to a recent study the greatest opportunity for these therapies may be in patients at an earlier-stage of the disease, for which effective therapies have the potential to increase cure rates[87]. Similarly, a European Commission paper stated that PrO treatments offer 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[7]. Overall, incremental benefits of PrO treatments have been reported in the available evidence and are expected to have a large positive impact on patients' quality of life. However, as we are only at the beginning of the scientific journey to genomic- and biomarker-informed treatment, the breadth of clinical benefits and health system efficiency due to the uptake of PrO treatments is still under investigation.

5.6.2 Socioeconomic Impact

Beyond the clinical benefits offered by PrO treatments, these new innovative technologies can have a substantial socioeconomic impact. The socioeconomic benefits of PrO therapies are threefold and include: (i) delivery of better treatments for patients (see previous section); (ii) delivery of benefits to healthcare systems and society; and (iii) more efficient development of novel medicines ensuring more effective, efficient and ethical clinical trials[7]. At the healthcare system level, PO (i) facilitates better prediction of disease, using genetic data retrieved by companion diagnostic tests; (ii) ensures better disease management; (iii) reduces hospitalisation; and (iv) helps prevent or delay more expensive care costs, allowing scarce healthcare resources to be used most efficiently[7]. For instance, the estimated cost of lost productivity in early-stage breast cancer was €602 lower for patients undergoing genetic testing prior to starting chemotherapy[8]. Oncotype DX had an impact on effective use of health resources through the avoidance of unnecessary chemotherapy in breast cancer care[143]. In France, in 2013, about 300,000 patients were hospitalised with chemotherapy. However, with the increasing use of PrO therapies, there has been a decrease in the overall number of stays, including both public and private hospitals, of just under three per cent[8]. Dutch oncologists reported that the mean hospital stay for patients treated with PrO therapies is about three to four days compared to one week for patients who are treated with chemotherapy[15].

As well as reduced hospital stays there are indirect savings to be made. For example, analysis has shown that the mean incremental savings to society per patient receiving bevacizumab plus chemotherapy treatment for NSCLC was €2,277 in Italy, €2,695 in Spain, €3,350 in France and €4,461 in Germany. PO was found to yield more savings compared to standard chemotherapy in terms of increased productivity and decreased social benefits paid to patients who were able to return to work in France, Germany, Italy, and Spain[144].

5.6.3 Impact on Healthcare Budgets

Use of targeted treatments can potentially lower the overall cost of healthcare even though expenses may appear higher in the short-term due to the additional costs of companion diagnostics. This is because therapies accompanied by diagnostic tests ensure access is limited to patients who are more likely to benefit from the treatment in question, reducing potential financial waste from incorrect use[83]. For instance, the companion diagnostic used to ascertain whether patients with breast cancer have an overabundance of the HER2 protein costs around $400. Even though this might be quite costly, identifying which patients should and should not be treated with targeted treatment can save tens of thousands of dollars per person[142]. Therefore, using biomarkers to target therapies can be considered as a way towards a

more efficient and cost-effective healthcare system[62].

Overall, annual healthcare savings can be considerable if patients are offered targeted therapies based on genetic tests and their suitability with the targeted treatment, resulting in better prediction of response to treatment, reduced potential for adverse events and reduced wastage of health resources associated with treating non-responders[39,145]. System diagnostics including various biomarkers may add substantial clinical and socioeconomic value by being easily scalable to address much larger groups of patients, by comprehensively breaking down a single complex disease into multiple targets with tailored treatment options and by administering treatments only to patients who are more likely to benefit from it[35,41,71]. According to a white paper, the efficacy rate of personalised treatments is estimated at 50%, putting the global annual waste from misdiagnosis at about $350 billion[146]. Similarly, the French Cancer Institute has shown that molecular testing can produce significant savings, as the costs of testing are more than offset by reduced non-effective prescribing and its consequences[67]. Molecular testing before first- or second-line treatment initiation in French patients with NSCLC resulted in better survival with limited additional costs. In the scenario the incremental cost-effectiveness ratio (ICER) was €8,308 per life year saved (LYS) compared with standard care[147]. Similarly, a total of $604 billion could have been saved annually if patients with metastatic colorectal cancer received genetic tests for the *KRAS* gene and were then treated appropriately[6]. A disease-specific economic model for breast cancer showed that a 37% reduction in total treatment costs could be realised without affecting the average QALY by early stratification of women based on age, history and genetic profile. However, these savings would only be realised if the infrastructure for diagnostics and electronic health records was in place[41]. In France, savings of €30,000 on treatment were achieved in patients with colon cancer carrying KRAS mutations, who do not respond to EGFR antagonists, when they were first screened for EGFR status[56]. Similarly, by spending €1.7 million on EGFR mutation testing, €69 million was saved on the cost of gefitinib in patients with NSCLC cancer who would not benefit from receiving the drug[76]. These figures were recently updated to show that, between the period 2008 to 2014, a total of €459.6 million was saved on treatment with an expenditure of just over €11 million[148].

5.7 Stakeholder Engagement

Innovations in PO bring challenges for all involved stakeholders including patients, physicians, regulators, HTA agencies, diagnostic providers and pharmaceutical and biotechnology companies, both individually and as a network. The patient perspective is gaining prominence and it is increasingly considered in the reimbursement decision making process[149]. However, this still represents a challenge as in many European countries patient organisations and wider civil society do not have a role in the HTA process[150]. PO may increase patient's awareness of access and reimbursement issues, for example the HTA process. However, according to key stakeholders in Europe, we are still far from a goal of full patient understanding in this context[31]. However, the EMA has made progress in increasing patients' participation in regulatory processes and incorporating their preferences into the scientific process[34].

It is increasingly understood that patient organisations as a whole can play a fundamental role in increasing clinical understanding around biomarker testing and the impact of PO via the development and utilisation of educational material to enhance health literacy[31,151,152] .

5.7.1 Education of Physicians Around PO

Over and above patients, further training is needed around the concept of PO for physicians, and particularly oncologists in some contexts. A self-reported questionnaire showed that, across a number of specialities, about 36% of Canadian physicians were not familiar with the concept of PM[138]. Similar surveys in the USA reported that only 10% of American physicians felt adequately informed about pharmacogenomics testing, and that one of the main reasons for not utilising this kind of testing is the perceived uncertainty of clinical value[38]. There is a requirement for a similar, European focused survey to analyse the opinions of oncologists and clinicians practicing in the

region. A challenge for PO implementation is represented by conservatism of physicians in clinical practice[53]. Physicians may be reluctant to employ PO due to a general hesitation around novel technologies, even if they can lead to improved outcomes[53]. Furthermore, physicians may be not trained on or informed about the most recent innovations. Physician training is essential to move from a traditional reactive medicine model towards a proactive approach, where there is the need to interpret novel and different sources of information[35]. In this case clinical guidelines and seminars can be fundamental[31]. However, as of today most of the health workforce is still not actively required to use PO treatments[31].

5.7.2 Stakeholder Collaboration

Key experts in Europe also agree that other stakeholders (manufacturers, regulators, HTA bodies) do not collaborate effectively or sufficiently and communication in relation to PO can therefore be lacking[31]. Collaboration could improve patient access by aligning all key stakeholders towards common guidance and methodologies in Europe[7,116]. The European Parliament has recently voted in favour of the EU's future public health strategy post-COVID-19, which goes towards the idea of creating a European Health Union that could harmonise standards for quality of care and regulation[153]. There is evidence of a lack of collaboration across sciences, networks and stages of the development chain, and that medicines development could benefit from cross-disciplinary and cross-border collaboration in research[154]. Discussion between key stakeholders could also encourage the realisation of a common perspective on the concept of value of PO and genomics[31,71]. A common perspective could lead to consensus around evidence requirements for regulatory and reimbursement decisions, and on the quantification of the value of diagnostic tests to avoid inconsistency in coverage decisions[71]. Innovations related to PO may also require the development of key skills from clinical pathologists, laboratory analysts, molecular geneticists and informaticians, roles which are generally under-represented in health systems[155–158].

To summarize, knowledge gaps are still present across all stakeholder groups. Further collaboration and an increased effort to publicise the innovations brought about by PO is needed[31]. Consensus around the value of PO, regulatory approval procedures, pricing and reimbursement processes and requirements may also encourage development and implementation of these technologies, although competing interests among key stakeholders persist[31].

5.8 Country Case Studies

Using information from the literature review and primary data we analysed issues around the use of PO in more detail in five countries – England, France, Germany, Poland and Sweden. Background information on cancer care for each country is included in Appendix 3.

5.8.1 England

There has been significant endorsement of PM at the highest political levels for more than a decade in England leading to a national strategic vision of PM adoption by the NHS[6]. In 2012, the UK began a two-year pilot programme to highlight the ability of the NHS to offer molecular diagnosis routinely for all cancer types. The Stratified Medicine Program's aim was to help establish a national service to "*ensure standardized, high-quality, cost-effective genetic testing of tumours is available for people with cancer*". Initially, 9000 patients had tissue samples from breast and prostate cancer tested for specific genetic mutations and variations[146]. The national infrastructure for cancer genomic testing has now evolved beyond this model[159]. England was the first country in Europe to launch a program dedicated to WGS via Genomics England which aimed to sequence 100,000 whole genomes from patients via 13 Genomics Medicine Centres, an aim that was achieved in 2018. Current policy aims are clearly focused on integrating genomics and diagnostics across NHS services for maximum impact on patient outcomes[7] and a recent Government report on the future of genomic healthcare confirmed the UK government's ambition to, over the next ten years "….*create the most advanced genomic healthcare system in the world, underpinned by the latest scientific advances, to deliver better health outcomes at lower cost*" by becoming the first national healthcare system in the world to offer WGS as part of routine care and sequencing half a million genomes by 2023/24 via the NHS Genomic Medicine Service for England[160].

As a result of these advances access to PrO medicines has improved over the past decade. In 2019 a survey of 1000 surviving cancer patients conducted by the Institute of Cancer Research showed that over a third of survivors in the UK had received state-of-the-art targeted drug treatment or immunotherapy. Figures were particularly impressive in melanoma, where two thirds of patients had received immunotherapy (versus just 5% receiving chemotherapy) and leukaemia, where over half received targeted drugs (versus just 43% receiving chemotherapy)[161].

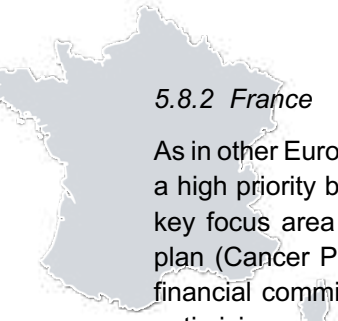
Despite this, access to certain PrO treatments has faced numerous challenges meeting required cost-effectiveness thresholds to achieve positive HTA body recommendations. Stakeholders were of the opinion that cost, or perceived lack of cost effectiveness, was one of the main barriers to further PrO utilisation despite the fact that England is seen by some to have relatively lower prices than some other European countries due to the methods of commissioning. One stakeholder thought that the general cost control culture of the NHS restricted medicines availability to those that we have good evidence for. Whilst not necessarily a negative this may limit access to certain medicines compared to other European countries with less stringent cost control processes. The centralisation aspect of medicines reimbursement, whilst ensuring equal access to all patients in England, can have a certain 'clunky' element which is not necessarily agile and reduces availability to an 'on' or 'off' switch with no regional variation[31].

A number of policies have been introduced to improve and expedite access to innovative medicines like PrO. For example, the Cancer Drug Fund (CDF), established in 2011 to fund medicines not routinely funded by NHS England due to cost issues. Similarly, in 2014 the UK regulator (the MHRA) also introduced the Early Access to Medicines Scheme (EAMS), supporting access to medicines whilst the regulatory process is ongoing. Pembrolizumab, for melanoma, was the first product to be launched through EAMS, giving more than 500 patients in the UK early access.

Although stakeholders interviewed as part of this project were of the opinion that, whilst England "talks a good game", the reality is that cancer outcomes have not been as good as some other countries. Some were concerned that this may be due to the rationing of companion diagnostic tests[31] but despite these concerns, the uptake of companion diagnostic testing is relatively good. BRAF+ test adoption sits at 56% in the UK, in

contrast to 45% in France and the UK has the highest uptake of NGS for oncology with 52% of labs offering it, significantly higher than the EU average of 17%. By 2020 England is expected to have NGS diagnostic capacity for 70,000 patients a year[7]. Furthermore, all physicians in England have access to a list of 978 nationally reimbursed diagnostic tests, covering almost 200 different cancer types.

As far as more novel, modern products like tumour agnostics and immune modulating products are concerned England's response is generally positive. Both larotrectinib and entrectinib (two tumour agnostic therapies) are now available for use within the NHS[162,163] and there is long standing support for tumour agnostic therapies[164]. Furthermore, patients in England were among the first in the world outside the USA to receive CAR-Ts outwith clinical trials due to NHS preparation specific to their unique challenges in advance of their approval and marketing. It was hoped that this early and efficient access to CAR-Ts in England had set a precedent for subsequent innovative products, but it seems that the issues around pricing and testing technology have had ramifications.



5.8.2 France

As in other European countries, PM has been given a high priority by the French Government and is a key focus area within the national cancer control plan (Cancer Plan). This has ensured continuous financial commitment to support key objectives in optimising cancer care (i.e., promoting early diagnosis and testing) and has led to a very favourable environment to ensure France leads the way in the uptake and adoption of PO[7]. Whilst the Cancer Plan ended in 2019 and has not yet been renewed there will be a new ten-year strategy from 2021, where early diagnosis and testing, particularly in the fight against undiagnosed cancer, will be key objectives.

As early as 2006 a national network of 28 hospital molecular genetics platforms was implemented. In 2009, 160,000 genetic tests were performed on 102,000 patients[165]. Stakeholders discussed the merits of this system – all solid tumours and haematological malignancies are tested for biomarkers. France's recent Genomic Medicine Plan confirms that the country aims to become a leader in PrO and PM utilisation. The goal is to provide whole exome sequencing for patients with no known classical genomic alterations and no clear treatment option. France also aims to integrate genomic medicine into the care pathway and provide access to genomic testing, and PM products, for all patients with cancer or a rare disease by 2025[166]. This target was facilitated with the opening of 12 sequencing centres and a €670 million injection from the French Government[7]. The first two centres include the SeQOIA project in Ile-de-France and the AURAGEN project in the Auvergne-Rhône Alpes region[167].

Timely access to PrO medicines has largely been facilitated by the 'Autorisation Temporaire d'Utilisation' (ATU) (which will evolve from July 2021 to become an 'early access' mechanism) introduced to allow patients with an unmet clinical need to receive early access to medicines that have not yet received marketing authorisation. In the past ten years almost half of targeted therapies were available through an ATU, granted on average 160 days before the relevant MA. For non-small cell lung cancer the ATU process allowed access to gefitinib five years before EMA approval, crizotinib two years before EMA approval and ceritinib one year before EMA approval[7]. Similarly, as of the end of 2015, most indications (95%) for targeted cancer therapies have been given a favourable opinion by HAS (the French National Authority for Health (Haute Autorité de Santé) the body responsible for performing HTA) with 75% of them having demonstrated a clinically and statistically relevant effect and provided quality data with a satisfactory methodology. In the hospital setting the majority of innovative therapies are present on the 'liste en SUS' (although there are exceptions) where prices are negotiated at a national level between the CEPS (Comité Economique des produits de santé, the body responsible for the negotiation of medicine and diagnostic prices) and the manufacturer[7].

In terms of diagnostic testing, despite a potentially slow start – the HER2 test was authorised in 2000 but did not receive a positive reimbursement decision in the country until 2007[71]. France now spends more on in vitro diagnostics than the Netherlands, the UK and Poland (although less than Switzerland, Germany and Denmark)[7] and aimed to be capable of sequencing 235,000

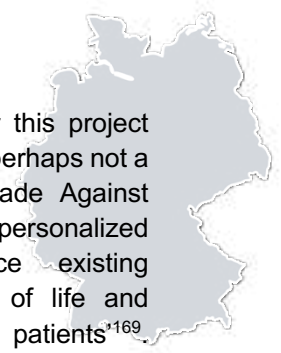
genomes per year by 2020. Recently, INCa (the Institut National du Cancer) spent €1.7 million testing for EGFR biomarkers in over 16,000 lung cancer patients. Results showed that around ten per cent of those tested would respond to available treatments (gefitinib or erlotinib). By not treating the ~15,000 non responding patients savings of €69 million were made[76]. Between the period 2008 to 2014 analysis showed that a total of €459.6 million was saved on treatment with an expenditure of just over €11 million[148]. In 2012 it was reported that setting up a network of 28 hospital molecular genetics platforms to perform similar molecular diagnostic analysis of cancer patients reportedly saved a total of €354 million, versus the €4.2 million of public funding required for the testing. On average there is at least one of these hospital-linked centres per administrative region, acting as a collaboration between university hospitals and cancer centres and performing diagnostic testing via commercially available in vitro diagnostic test kits and laboratory-developed validated testing approaches.

Despite these specialist centres research shows limited access for specific prognostic/diagnostic multianalyte assays in France. To counter this the MoH recently introduced reforms to streamline diagnostic access, forcing both public and private institutions to integrate the reimbursement of diagnostics in the hospital DRG system. Furthermore, in 2015 the Ministry created an innovation fund – the RIHN (Referentiel des actes innovants hors nomenclatures) specifically for novel diagnostics to facilitate access to conditionally approved products. As of 2018 four molecular signatures (Oncotype DX, PAM 50, Endopredict and Mammaprint) had obtained conditional access via this mechanism[7], although stakeholders mentioned the existence of delays for inclusion of tests such as Oncotype DX into general care, potentially impacting patient care[31]. Furthermore, the fund has been capped at around €380 million since 2015 and is not increasing in line with the growth in available biomarker tests[168].

Like England, the French government has commitments towards prioritizing the development of NGS infrastructure through clear policy recommendations and targets. This has been a priority for France since 2012/2013 with the first national structuring project coordinated by INCa in 2013.

Despite the positive focus on PO evident in France challenges remain. As PO is advancing, cancer care is shifting towards further stratification in multiple rare cancers expressing specific molecular targets. Within this new paradigm, the feasibility of large RCT measuring long term disease outcomes becomes more limited. As mentioned previously basket trials have emerged as an alternative for clinical development of targeted therapies. However, the level of evidence at time of market approval can be perceived as limited, especially to support pricing and reimbursement decisions. In the last five years, reimbursement has been denied for several indications of targeted therapies. Diagnostic testing of patients is highly correlated with whether or not a targeted therapy is available and recent access challenges for those drugs together with the capped funding of diagnostics tests illustrate that there are still barriers to optimal access to PO in France despite the fact that it is identified as a key public priority.

5.8.3 Germany



Despite stakeholders interviewed for this project feeling that personalised oncology is perhaps not a national priority[31], the German Decade Against Cancer aims to 'develop new personalized treatment methods and advance existing treatments to enhance the quality of life and survival prospects of cancer patients'[169]. Furthermore, the use of targeted oncology therapies in Germany has tripled since 2009[51]. Germany now has the highest use of innovative medicines PD-1 and PD-L inhibitors after the USA, with a more than two-fold higher use than the UK. Of those countries under the EMA, Germany has access to the most oncology medicines launched between 2012 and 2016, in large part due to its 'free pricing' from launch (where a company can set their price for a year before a new price is determined by HTA assessment). Thirty-nine oncology medicines launched between 2013-2017 were available within two years of global launch, versus 17 in Poland for example. Only 11 out of a possible 55 were not available as of 2018[170]. Stakeholders interviewed as part of this project were of the opinion that access is better in Germany than other European countries due to three factors: 1.) The large role played by federal structures steering healthcare provision states in

determining healthcare provision; 2.) Hospitals are relatively free to use products from a treatment portfolio as they wish so, like France, physicians retain significant discretion and can prescribe any authorised product; and 3.) There is 'free pricing' available at launch enhancing access[31].

Utilisation of PO in Germany has been shown to have an impact on healthcare costs. Research in 2012 showed that, as a result of the use of bevacizumab for non-small cell lung cancer, Germany saved €4461 in terms of societal costs (compared to standard chemotherapy) through increased productivity and decreased social benefits paid to patients. The equivalent figures were €2277 in Italy and just under €3500 in France[7].

In the outpatient setting there is a lack of reimbursement for testing[171] but in the hospital setting companion diagnostics are paid for via a pre-determined fixed payment rate per case according to historical patterns, not the additional cost of using a test. It is possible that hospitals could view companion tests as an extra expenditure creating a disincentive for adoption[121]. There could also be access delays due to procedure code generation (this is also the case in the ambulatory sector). To bridge such gaps a temporary funding process – the new diagnostic and therapeutic procedures" (Neue Untersuchungs-und Behandlungsmethoden – NUB) – has been created for products that have just been launched in the country. Although to date, all NUB applications for diagnostics and testing have been rejected in the field of oncology[171].

Like other countries Germany has tried to simplify the process of evaluating companion diagnostics but there tends to be no standardized approach[83]. Despite this Germany spent around €27 per person on in-vitro diagnostics in 2016, higher than Poland, the UK, France, Spain and Italy among others[7]. As far as innovative diagnostic processes are concerned Germany has been rather behind the curve in comparison to the rest of Europe. It has been described as one of the slowest European markets to adopt NGS with only seven per cent of clinical molecular diagnostic laboratories using NGS[7]. To counter this Germany is in the process of establishing several new NGS centres of excellence to be operational towards the end of 2020[116] and the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte - BfArM recently updated the OPS (Operation and Procedure Classification System) coding catalogue to include NGS thus paving the way for hospital reimbursement [172].

Looking to the future and the adoption of novel innovative medicines like tumour agnostics and CAR-T therapies, the German Society for Haematology and Clinical Oncology (DGHO) prepared a draft guideline around the approach to tumour-agnostic treatment, which was due for consultation at the end of 2019[116]. Despite this, in April 2020 the Federal Joint Committee (Gemeinsamer Bundesausschuss – G-BA) determined that larotrectinib gave no added benefit[173].

Novel CAR-T products will benefit in Germany from their orphan drug status - they will neither be referenced priced nor have to submit full HTA dossiers and AMNOG, the Act on the Reform of the market for Medicinal Products (Gesetz zur Neuordnung des Arzneimittelmarktes), automatically assumes proven benefit, provided sales over the preceding 12 months do not exceed €50 million – extremely rare given the small population sizes involved[38]. This will be crucial to the success of CAR-T therapies (and other precision oncology products) due to the restrictive nature of regulations around clinical trial designs and the fact that single-arm trials are frowned upon[30]. To prepare for the emergence of these high-cost agents, in January 2018 the G-BA removed an exemption from its HTA system where medicines used solely in the hospital setting did not have to undergo a benefit assessment and payers indicated that high prices and high levels of uncertainty associated with CAR-T therapies mean they are pushing for outcomes-based agreements, something that Germany traditionally shies away from[30].

5.8.4 Poland

There is no stand-alone national plan focused on PO and there is limited reference to PM or gene therapy in the National Oncology Strategy (The Cancer Plan). Pilot projects in 2018 saw the development of a number of new hospital networks, set up as linked groups with long term contracts to deliver patient services. These

'National Oncology Network' centres of excellence concentrated expertise, funding and infrastructure to enable increased use of PrO[7]. Stakeholders spoke of recent transformations of hospitals into 'National Institutes of Oncology' and a general increase in focus around PO[31]. There is also an active Polish Coalition of Personalised Medicine which organizes a number of activities, publishes reports and obtains system data around PO.

Despite this apparent focus, in terms of access Poland had very limited uptake of a number of products such as ipilimumab, afatinib, erlotinib and gefitinib[1]. The recent Oncoindex[iii] stands at -63. This means that out of the 114 medicines registered within the last 15 years and recommended by ESMO, only 27% are reimbursed. Of the remainder, 29% are reimbursed with limitations and 44% are not reimbursed at all. The index is the first portal to demonstrate the level of reimbursement of cancer medicines registered in Europe since 2004 and recommended for use by the ESMO in Poland[174]. Recent analysis by Alivia compared sales of 30 selected innovative cancer medicines across 13 European countries. For all but two of the products (vemurafenib for melanoma and lapatinib for breast cancer) utilisation levels, calculated as sales level, in Poland are lower than the mean sales across the 13 countries of interest. Mean medicine prices were also found to be lower in general than other countries in Europe[175], although stakeholders were of the opinion that some innovative medicines were priced highly, leading to lower availability in the country[31]. In terms of specific availability, the analysis showed that only two products were available via the reimbursement system without restriction in contrast to 30 in the Netherlands, 25 in Switzerland and 15 in the UK. IQVIA has also recently shown that Polish cancer patients have limited access compared to other countries. Looking at a selection of 54 oncology medicines launched between 2013 and 2017, only 24 were available as of 2018. In Germany the equivalent figure was 39[170]. The recent EFPIA WAIT indicator shows that the rate of availability for oncology products in Poland was 37% in 2019, versus 98% in Germany. Polish cancer patients had to wait on average 781 days between EMA marketing authorisation and availability within the country, versus 35 days for German patients[132].

Precision medicines in Poland are available as part of a specific service financed by the National Health Fund (NFZ). Every two months the MoH publishes a list of medicines financed from public funds[31]. Poland spends around €2.6 billion on drug reimbursement, around ten per cent of which is on new, expensive patented medicines. In 2015, expenditure on innovative cancer medicines represented less than a fifth of the total NFZ spend on innovative medicines. As a result the main financing channel for innovative cancer medicines is via treatment programs[176] which increased in number from 69 in 2015 to 92 in 2018, largely due to oncology products[177]. Eligible patients must meet the criteria included in the programme description for entry into the drug programme and healthcare services under the drug programmes are separately contracted by the NFZ. In 2015 over 20,000 patients were included in one of these treatment programmes in order to gain access to innovative cancer treatment, and in 2018 a total value of $483 million worth of oncology drugs were reimbursed by the programmes (the equivalent value for non-oncological drugs was $438 million)[177].

As far as molecular genetic testing is concerned Poland does not do as well as western European countries, although it is one of the few countries where molecular profiling is marketed directly to patients allowing them to pay out of pocket[139]. Furthermore, there is a private market for specific tests like the MammaPrint, available as a privately ordered test from laboratories in the country. Analysis by Wilsdon (2018) shows that in 2016 Poland spent €8.8 per capita on in vitro diagnostics, in contrast to €56.3 in Switzerland and €15.3 in the UK. The financing of testing services is generally integrated into hospital budgets, covering funding by a DRG-type system or existing block grants. For example, the HER2 breast cancer test is predominantly performed by hospital-based pathology labs which can create challenges for the introduction of novel tests. Not only is investment in infrastructure required but there is a need to ensure that existing reimbursement rates sufficiently cover the cost of novel tests. In terms of novel methods of testing, specialist cancer centres (such as the Maria Skłodowska Curie Institute) are at the forefront of the development of NGS methods for detection of genetic abnormalities related to breast cancer[7]. The country is now

working towards the introduction of a quality assessment model related to accessing testing and the application of diagnostic technologies[31].

Stakeholders mentioned the legal issues concerning the increased adoption of PO in Poland. Legislative solutions, such as the modification of the Pharmaceutical Law Act and the Reimbursement Act, are required to properly define gene therapies and access requirements. As in other countries there is a need to create an up-to-date and fit-for-purpose model which will take into account the reimbursement of specialized genetic and molecular tests necessary for drug administration.

5.8.5 Sweden

National policies related to the future of cancer care in Sweden highlight that PO is becoming more valuable to the country, despite some stakeholders being of the opinion that it was not necessarily an early adopter of advances in molecular profiling[31]. In general, there is a healthy appetite from government to create an environment suited to the utilisation of health data in order to leverage the use of RWE, both as a tool for introducing innovative therapies and an enabler for PM. Furthermore, PM is prioritised in the government's Life Science Strategy and is an area of targeted focus due to the numerous well-developed registries and the advanced state of research on patient reported outcomes and RWD. The government Life Science Office has a clear position to maximise the use of health data. The challenge lies in ensuring treating oncologists utilise the broad range of biomarkers and diagnostics available in order to incorporate PO into their everyday practice.

'Vision Zero Cancer', an initiative developed in November 2019 by a group of companies and organisations plus the Stockholm School of Economics, aims to make Sweden a world-leader in terms of preventing, detecting and treating cancer with the help of significant collaboration between academia, business and all players in the cancer eco system[178]. Similarly, Genomic Medicine Sweden (GMS) was founded in 2018 with the aim of translating innovation in genomics into clinical practice to develop a sustainable infrastructure for the future of PM in Sweden. The first phase saw it focusing on cancer as one of its three areas of specific interest where it aims to implement targeted diagnostics for mutations in approximately 500 cancer genes in routine cancer care, pilot a global diagnostics project and establish a national standardised tool set for standardised diagnostics in the country[179].

Sweden already performs around 10,000 small-medium NGS panels per year in routine clinical practice for patients with cancer and around 1500 whole genome sequencing panels within rare disease but GMS has an ambition to analyse up to 65,000 samples per year by 2023. To do this they are establishing a national informatics infrastructure to enable unified analysis, interpretation and sharing of genetic data in the country and develop a coordinated nationwide storage and sharing solution for patients' genetic data between the country's 21 regional healthcare authorities. Sweden is already well placed to maximise the potential of RWE as it is able to prospectively collect RWD from all consenting patients. Stakeholders highlighted the advantage Sweden and other Nordic countries have in terms of their personal identification numbers which allow patients to be tracked within the healthcare system[31]. The National Patient Summary, initially rolled out in 2009, collected 300,000 samples in its first year but has rapidly expanded over the last decade. The ability to use this country-wide patient information database for tracking care decisions and outcomes would allow the benefits of novel PrO medicines and associated CDx to be determined.

Stakeholders also discussed the fact that TLV (the Dental and Pharmaceutical Benefits Agency responsible for determining whether or not a pharmaceutical product or device will be subsidised by the state, performing HTA on medical devices and regulating the pricing and reimbursement of medical device consumables) along with the government, are aware of the need to look into the QALY and HTA methods used when it comes to innovative products and that a paradigm shift is required. They are currently drafting two reports on precision medicines, one focusing on the complexities of introducing these products into the niche market and one looking at issues around RWE. Stakeholders also spoke of the potential 'post code lottery' due to the fact that each of the 21 regions have control of healthcare

provision[31]. The New Therapies (NT) Council, a group of experts supporting Swedish regions on questions concerning new therapies, aims to ensure equal access to medications for all patients throughout the country by making recommendations to the regions on the use of novel therapies based on the framework of TLV evidence analysis. However, as these are only recommendations it is then up to the regions to decide to what degree these will be followed which results in geographical access variation persisting.

As in other European countries Sweden has a form of managed entry agreement available which may be considered by TLV between regions and a pharmaceutical company when deciding on pricing and reimbursement. The first oncology medicines to be approved via MEA in Sweden were enzalutamide and abiraterone acetate for prostate cancer in 2015. By the end of 2016 there were a total of 16 products, across six therapeutic groups, enjoying MEA[180].

As TLV also has responsibility for evaluating diagnostics it recently published recommendations for the FoundationOne diagnostic (the first FDA-approved tissue-based broad NGS-type companion diagnostic which tests for mutations in 324 genes for guiding treatment of several solid tumours including breast cancer and non-small cell lung cancer). TLV was unable to perform a cost effectiveness evaluation due to the large number of alterations the test covered. The recommendation was therefore based on cost comparison instead. At €2000 per test TLV found that it was cost-effective in some situations but not others. As a result clinicians and healthcare providers are able to find a role for it in certain situations but it is not approved for general daily practice[1,31].

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6. POLICY RECOMMENDATIONS

Innovation in the PO arena has the potential to significantly improve patient outcomes and foster patient-centred care. A favourable policy environment will be needed to maximise the potential future impact of PrO medicines. Based on current evidence we have elaborated a set of policy recommendations which sit within three 'buckets' for action

Stronger collaboration delivering transparent and well-informed, decision-making processes to advance and implement PO in European cancer care

1. European strategy on PO use in Europe, including a roadmap for change setting out basic principles and objectives for the future with enhanced levels of European harmonisation and supported by appropriate resources.

2. Regulators and HTA bodies collaborate closely to ensure transparent, well-informed decision-making processes and alignment on principles supporting innovation and encouragement of enhanced patient access by allowing both regulatory approval and reimbursement based on unmet clinical need and surrogate endpoints.

3. Patient associations, advocacy groups and clinicians to work towards giving health literacy a higher priority so patients feel empowered as advocates for the integration of PO into their care.

Improvements in institutional structures to secure access to new PrO medicines and biomarkers

4. All eligible patients should have access to fully reimbursed, actionable mutation (biomarker) testing built into standardised patient pathways at diagnosis and disease progression.

5. Streamlined and predictable regulatory procedures for PrO medicines, harmonised across the EU, to embrace new trial designs and statistical methods, including genomic driven designs (e.g., basket and umbrella trials) to account for the PO paradigm of very small patient populations.

6. Acceptance by HTA agencies of newer trial designs (e.g., basket and umbrella trials). Additionally, the EUnetHTA model should incorporate a PO pathway specifically focused on new models for evidence generation.

7. Assessment of value to move towards broader long-term concept of overall economic value, taking into account the total value of personalisation and considering the costs offset by, for example, 'ruling out' ineffective treatment options.

8. Ensure timely and simultaneous evaluation and reimbursement of both PrO medicines and biomarker tests.

Investing in appropriate infrastructure that expedites the delivery of PO

9. Development of a European Institute to translate laboratory-based research findings into effective and affordable medicine. For example, a 'PO accelerator programme' for the transfer and translation of ideas from academia to patients, following the examples of available best practices.

10. National governments should invest in diagnostic standards and infrastructure, particularly that required for next generation sequencing, and develop dedicated funding pathways to ensure access to diagnostics for all.

11. Development of Europe-wide biobanks, with EU standardisation, for tissues and biofluids supported by nationally funded high-quality patient registries is urgently needed.

12. EU harmonisation of ethics approvals to allow the sharing of anonymised, protected patient data in a pan-European network based on appropriate informed consent procedures.

13. EU funding to encourage connectivity between the clinical community, -omics experts and quantitative scientists to effectively deal with 'big data' resulting from registries, bio-banks and other RWE related sources. Plus, the incorporation of systems to support 21st century medicine and provide methods for effective collection and analysis of data.

14. Incorporation of 'up-to-date' information relevant to PO in undergraduate and postgraduate courses for all healthcare professionals as well a mechanism that incorporates education and knowledge around scientific advancements relevant to PO into compulsory continued professional development (CPD) for practicing clinicians.

15. Timely update of clinical guidelines to reflect the latest advances in both diagnostic testing and PrO medicines, as well as implementation of these guidelines by clinicians.

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8. APPENDICES

8.1 Appendix 1 – Full Methodology

Literature Review

Systematic Literature Review: Data Sources, Search Strategy and Keywords

The previously identified analytical framework was used to develop a keyword search strategy including a number of general and policy-specific keywords and allowing for all synonyms and different phrasings of all search terms to be captured. This keyword search strategy was then used to search databases including Web of Science, Ovid Medline, ProQuest and Scopus. Where possible the search was restricted to keywords present within the abstract and title only to limit the number of irrelevant papers being returned. In some specific situations keyword searches that would have been predicted to return a number of results, for example, "personal* oncol* AND HTA" returned zero papers. As a result, in instances where "personal* oncol* AND {additional search term}" returned zero results we used the alternative "personal* medicine AND {additional search term}". Papers were limited to English and those published between 2000 and June 2020.

We also completed a targeted and comprehensive search for grey literature from sources including Google Scholar, WHO, ISPOR, European Commission, EFPIA, Office of Health Economics, European Biopharmaceutical Enterprises and the European Alliance for Personalised Medicine. Key words used for these searches were "Personalised Oncology AND Europe". Relevant information was recorded and combined with the results of the systematic literature review. Finally, additional literature gathered from contacts was also included.

Study Selection, Data Extraction, Evaluation and Synthesis

Results were filtered based on the relevance of the title and abstract to the topic. Those that were considered relevant were read in full. Papers that discussed any aspects of any of the pre-determined endpoints were included in the final data set. Data relevant to the analytical framework was extracted to a database for further analysis. A comprehensive synthesis of the literature was then carried out to identify key trends related to PO use across Europe.

Primary Data Collection

The rapidly evolving nature of personalised oncology indicates that current literature may not accurately reflect either recent levels of utilisation or the latest challenges. We therefore collected primary evidence using a semi-structured interview technique, allowing us to fill any gaps from the literature review. It also allowed us to gather the perspective of a number of different stakeholders and report on country-specific practices and policies that may not yet be reflected in currently published literature. Primary evidence was gathered via semi-structured interviews with key stakeholders from five countries across Europe – England, France, Germany, Sweden and Poland. The interview tool can be seen in Appendix 2. Stakeholders included representatives from government agencies, industry representatives, patient representatives and academics, all of whom expressed personal views on the implementation of PO in their respective countries.

Case Study Development

In order to delve deeper into the landscape for PO across Europe we implemented a case study-based analysis across five countries. The selection of these countries was guided by input from the EFPIA member company representatives on the EOP (EFPIA Oncology Platform). The countries chosen (England, France, Germany, Poland and Sweden) represent different regions of Europe, offer varying levels of reimbursement mechanisms and have varying levels of prioritisation and policy in place for PO. Data from both the literature review and primary analysis was used to populate these case studies.

8.2 Appendix 2 - Stakeholder Interview Guide

General:

1. What comes to mind when you think of the phrase “personalised or precision oncology (PO)”? How would you define it?
2. Do you think PO is considered a national priority in your country? (i.e., is there a stand-alone national plan focused on personalised medicine, or is it considered in national cancer plans?)

Access:

3. To what extent are precision oncology medicines available in your country? To what extent are they used in your country?
4. To what extent are diagnostic genetic tests used in your country? Is there a difference in access between comprehensive genomic testing (i.e., next generation sequencing NGS) and single gene/small panel genetic testing?
5. In your opinion how do you think the level of access to PO in your country compares to other EU countries?
6. Do you think your country is maximising the potential value of PO?

Challenges/Barriers:

7. Are there barriers to the use of PO that you are aware of?
8. What do you think is the biggest challenge around the use of PO in your country?

Value:

9. How do you think the price of PO in your country compares to other countries in Europe?
10. Are HTA performed on PO medicines? What are the main criteria surrounding personalised medicines that are considered during HTA, reimbursement or pricing and/or funding assessments? Do you think these criteria are appropriate? How is RWE viewed by HTA bodies?
11. How are companion diagnostics dealt with in terms of HTA, reimbursement, pricing? Are they assessed alongside PO or separately? Does this impact patient access?
12. Are there clear funding mechanisms for PO and/or for diagnostic tests?

Stakeholders:

13. Do you think health professionals have enough training to ensure their clinical understanding around PO or genomic medicine is sufficient? Are there sufficient guidelines in place for physicians around the use of PO?
14. What do patients think of PO? Are patients well informed about PO – from either patient organisations or health professionals?
15. Is there sufficient collaboration between relevant stakeholders at the right stages during development? (i.e., payers, clinicians, regulators, pharma companies).

Potential suggestions/policy recommendations:

16. What do you think should be done to improve the use of PO?
17. What are your expectations around PO for the future?

Any other comments?

8.3 Appendix 3 - General Case Study Country Information

England

England has a tax funded universal healthcare system, providing a comprehensive service, available to all with access based on clinical need rather than an individual's ability to pay. Cancer care is organised in a 'hub-and-spoke' model where patients benefit from a cancer management strategy formulated by a multidisciplinary team across cancer units in general hospitals. IT system networks support electronic patient records and real-time data sharing allowing clinicians to collaborate to deliver effective services between both local and regional, more specialised centres. As a result, patients are only required to travel to the central hub specialist hospital when essential for diagnosis or treatment.

Cancer incidence is at 600 cases per 100,000 inhabitants, in line with the average for western European countries. The cancer mortality rate, at 162 per 100,000 inhabitants, is slightly higher than other western European countries, and the International Cancer Benchmarking Partnership revealed that the UK has significantly poorer survival rates for lung, colorectal and ovarian cancer than comparator nations such as Australia, Canada, Norway and Sweden, although time to diagnosis is in line with France. Total health expenditure per capita at €3145 (PPP) is lower than France, Germany and Sweden whilst, in 2018, cancer drug sales per capita were €49, almost €50 per capita lower than spend in Germany, although they accounted for 10% of EU cancer drug sales. A recent analysis by the OECD, looking at a number of oncology related product/indication pairs and their levels of access/utilisation in multiple countries, found that England does relatively well in terms of delay between first marketing approval and subsequent granting of coverage. The delay averages 20 months in England versus 24 in Belgium, 31 in France and 33 in Hungary [59]. The same analysis showed that, out of a combination of 109 oncology related product/indication pairs, England approved and covered 84%, in contrast to 82% in Belgium, 88% in Germany, 91% in Denmark and 76% in France. Comparing older 'vintage' and newer products – where the older products are included on the WHO Essential Medicine List and the newer products have been approved by the FDA since 2014 – England has better access to older products, approving and covering 94% versus 77% of the newer products. The EFPIA WAIT indicator[132] suggests a median time of 332 days between EMA marketing authorisation of an oncology medicine and the date of availability for patients in England, faster than the majority of European countries.

The overall economic burden of cancer was predicted to increase from €6.55 billion in 2008 to €28.87 billion by 2020 in the UK as a whole[181]. Analysis in 2010 predicted that, if by 2020 the UK had improved cancer survival rates to rival the best in Europe, cumulative costs could be reduced by €11.69 billion and over 70,000 lives could be saved. Recent global events have limited access to cancer care in the UK as the COVID-19 pandemic has intensified. Predictions suggest that, due to a near 'shut down' in cancer referrals and significant diagnosis delays, there is now a backlog of roughly 3 million patients waiting for cancer screening or diagnosis. Further discussion on the impact of COVID-19 on cancer care in Europe is beyond the scope of this paper.

France

France has a mandatory health insurance system covering the entire 67 million strong population and managed at the national level by the government and parliament. The cancer incidence rate in the country at 640 cases per 100,000 population is in line with other western European countries like the UK and Germany. Mortality rate, at 153 per 100,000 inhabitants, is lower than that of the UK and Poland and comparable to Germany. As in other wealthy European countries mortality rates for cancer have now overtaken cardiovascular disease. In terms of specific survival rates France does relatively well. In 2014, 5-year survival rate for breast cancer was 86.1%, amongst the highest in Europe. Similarly, the 5-year survival rate for lung cancer sat at 13.8%, higher than the UK, Spain and Denmark, although lower than Belgium, Germany and Poland[1].

Total health expenditure in 2018 was €3583 per capita (PPP), higher than the UK but lower than that of Germany and Sweden. The cancer specific share of this healthcare spend increased from around six per cent in 2013 to 7% in 2017 and currently equates to around €250 per capita, making it one of the European countries spending the most on cancer care. In 2008 the French National Health Insurance agency and the National Institute of Cancer (INCa), a body created in 2004 to provide early nationwide access to innovative molecular testing in the field of oncology, published for the first time details of the cost of cancer care in France[181]. Results highlighted the fact that cancer care costs were €14 billion, only three billion less than costs related to cardiovascular disease. By 2018 the direct economic burden of cancer reached €18 billion[1].

In 2007 France was the biggest spender on cancer medicines in Europe, alongside Germany, responsible for 25% of sales in Europe. At the time anti-cancer drugs were responsible for a fifth of the overall hospital spend on drugs, and accounted for less than 14% of the total cancer budget[181], although targeted therapy represented 57% of anticancer drug costs[146]. By 2018 the proportion of EU sales of cancer medicines that France was responsible for fell to 16%, likely due to price reductions put in place to control public spend following the 2008 global financial crash. It took until 2015 for cancer drug sales to rise above 2008 levels, increasing from around €50 per capita in 2008 to €77 in 2018. France now sits as the sixth biggest spender on cancer medicines in Europe behind the likes of Austria, Switzerland and Germany.

Access to cancer medicines is relatively good in France. Recent OECD analysis has shown that, of 109 cancer related product/indication pairs only seven per cent were not approved, in contrast to nine per cent for Denmark, 10% for the UK and 12% for Germany[59]. This is in line with reports from stakeholders who were of the opinion that access is amongst the top countries in Europe and that the country as a whole is maximising the potential value of PO medicines [31]. Of the newer products analysed by the OECD France approves and covers 58% of the 34 cancer related product/indication pairs, and approves, but does not cover 36% of the pairs. Approval levels are therefore in line with Germany, the UK, Sweden and Belgium. Time to access tended to be slower for France than either the UK or Sweden at 31 months between first marketing approval in the USA and subsequent granting of coverage in France[59].

Germany

Like France, Germany has a social security-based health system financed by mandatory fees paid by employers and workers through taxes. Around 90% of the population are covered by a statutory health insurance (SHI) provided via 134 SHI funds. The remaining ten per cent of the population is covered by private insurance. German federal laws set the framework for provision and financing of health care but details are delegated to decision-making bodies. The Federal Joint Committee (Gemeinsamer Bundesausschuss – G-BA), made up of physicians, hospital representatives, dentists, patient representatives and SHI representatives, is the central decision-making body responsible for regulation of reimbursement, assessment of new methods of medical examination and treatment, evaluation and classification of novel pharmaceuticals and publication of treatment guidelines[38].

In 2018 cancer incidence in Germany was amongst the highest in Europe, third only to Denmark and Hungary[1]. The cancer mortality rate at 153 per 100,000 inhabitants is in line with France and lower than both the UK and Poland. Five-year survival rates in Germany are amongst the highest in Europe. In 2015, the 5-year net survival rate for lung cancer was 15.6%, versus 10.3 in Demark, 13.8 in France and 14.4 in Poland. For breast cancer the equivalent figure was 83.6%, higher than the UK and Spain[1]. Total health expenditure is also amongst the highest in Europe at €4222 per capita (PPP), behind only Luxembourg, Norway and Switzerland. The cancer specific share of this healthcare spend increased from 6.3% in 2002 to 6.8% in 2015. It currently equates to €254 per capita, over €100 more per capita than the equivalent sum in the UK, making it one of the highest spending European countries when it comes to cancer care, along with Austria, Switzerland, France and the Benelux countries (Belgium, the Netherlands and Luxembourg). The direct economic burden related to cancer stood at €25 billion in 2018.

Alongside France, Germany was the biggest spender on cancer medicines in 2007, responsible for 25% of European sales at €2238.5 million. By 2018 this sum had risen to €7583.9 million, the highest spend in Europe by a significant margin, and 24% of European cancer drug sales[1]. This high spend on cancer medicines equates to high levels of access for the population. OECD analysis showed that, of 109 cancer related product/indication pairs analysed, 88% were approved and covered, behind only the USA and Denmark. Of those 32 pairs included in the WHO list of essential medicines, 97% were approved and covered whilst 94% of 31 newer pairs, approved by the USA FDA since 2014, were approved and covered[59].

Poland

Poland, the largest country in eastern and central Europe with a population of 38 million, has a social security-based healthcare system where healthcare is delivered via a publicly funded health care system, the Narodowy Fundusz Zdrowia (NFZ), free for all the citizens in the ‘insured’ category.

At 490 cases per 100,000 inhabitants, cancer incidence in 2018 was one of the lowest in Europe, ahead of only Romania, Iceland and Cyprus, more than likely due to the relatively low life expectancy figures experienced by Poland when compared with other countries in the region[1]. Despite low incidence levels,

mortality rates are high at 290 deaths per 100,000 inhabitants. Similarly, 5-year survival levels are lower than the European average. Generally, 54.2% of patients in Europe will live for five years with a cancer diagnosis. In Poland, this figure falls to 41%[176]. Looking specifically at breast cancer, 5-year net survival in 2015 was 71.6%, among the worst in Europe. In contrast, for lung cancer the figure stood at 14.4, higher than countries such as Denmark, Ireland, the Netherlands and the UK[1], although lung cancer mortality is still 83%, significantly higher than the European average of 56.4%[119]. This discrepancy could potentially be due to lag in diagnosis time. Diagnosis of lung cancer takes on average 6 weeks from first symptom in Poland, in contrast to three weeks in the UK and France[7]. Patients tend to be critical of the current referral system due to time taken for diagnosis and the lack of communication from healthcare professionals[182]. Stakeholders spoke of the 'Green Card' database, established in order to increase speed of diagnosis[31].

Poland spends six per cent of GDP on health, comparable to €1377 per capita, higher than only Romania and Bulgaria. The cancer specific share of this spend is around 7% of total health expenditure, equivalent to €96 per capita[1]. In 2018 the direct economic burden of cancer was predicted to be €2 billion, increasing from half a billion in 1995. In 2018 Poland spent roughly €15 per capita on cancer medicines, increasing from €7 in 2008. This makes it one of the lowest spenders on cancer medicines in Europe.

During the HTA process for pharmaceutical products manufacturers submit their HTA documentation to the Agency for Health Technology Assessment and Tariff System (AOTMiT), an advisory board to the MoH, which goes on to perform a HTA analysis for reimbursement. The cost effectiveness threshold sits at three times GDP per capita for one QALY (quality adjusted life year)[31]. In 2016 this figure was around €28,000[176]. Whilst this figure is relatively rigid it is growing yearly. Once HTA recommendations are made, negotiations take place between the manufacturer and the MoH. In general, clinical benefit and cost-effectiveness are the main criteria used in assessment. RWE is not accepted as guidelines focus on traditional RCT data. The current HTA process is guided by legal framework and is therefore seen as difficult to change. However, it is acknowledged by many stakeholders in the country that RWE is the future of HTA in some product types, and there are projects, not driven by MoH, looking at theoretical use of RWE[31].

Sweden

Sweden has a population of around ten million and a health system predominantly financed via taxes but with a radically different model to much of Europe due to the fully government funded, highly de-centralised system. Local taxes fund 70% of services with the Ministry of Health and Social Affairs establishing principles and care guidelines at a national level. The 21 regional councils are responsible for healthcare provision leading to potential discrepancies and 'post-code lotteries' related to healthcare delivery and financing.

At 570 cases per 100,000 inhabitants, cancer incidence in 2018 was slightly lower than countries such as the UK, Germany and France, although it is higher than Romania, Poland and Bulgaria (likely due to the lower life expectancies experienced by those countries). Cancer mortality rates are amongst the lowest in Europe, sitting ten per cent lower than the European average, whilst 5-year survival rates are also amongst the best in the region. For lung cancer, 5-year survival rates sat just below 20% (2010-2014), up from 12% in the period 1995-1999. For breast cancer, survival rates in 2015 were 86%, equivalent to France and higher than all other countries in Europe[1].

Total health expenditure at €4128 (PPP) is one of the highest in Europe, behind only Switzerland, Norway, Luxembourg, Ireland and Germany. The cancer specific share of this spend sits at €153 per capita (PPP) and only 3.7% of total expenditure – making it one of the European countries to spend the smallest proportion of their total health expenditure on cancer care. The most recent analysis put the direct economic burden of cancer in Sweden at €19 billion in 2018, up from €8 billion in 1995. Costs of cancer medicines in Sweden stood at just below €60 per capita in 2018, lower than a large majority of European countries but higher than the UK and Poland[1].

Despite this apparent low spend OECD analysis shows that of 109 cancer related product/indication pairs analysed, Sweden approved and covered 86%, behind only the USA, Denmark and Germany. Of 32 pairs included in the WHO list of essential medicines, 100% were covered and approved, whilst 71% of 31 newer pairs, approved by the USA FDA since 2014, were approved and covered, behind only the USA[59]. Access to medicines was also found to be generally efficient in Sweden with, on average, 23 months between first marketing approval in the USA and subsequent granting of coverage. Access is therefore substantially quicker than in France, but slightly slower than that of the UK[59]. The recent EFPIA WAIT survey suggests a median time of 203 days between EMA marketing authorisation of an oncology medicine and the date of availability for patients in Sweden[132]. Stakeholders spoke of the variation in access seen with positive and negative

reimbursement decisions. If a pharmaceutical product gets a positive reimbursement decision it can be available to patients as early as the next day. In contrast, if a product gets a negative reimbursement decision then the corresponding lag time may be as high as 500 days. This was not necessarily seen as undesirable. Stakeholders were of the opinion that the negative reimbursement decision obviously suggests that the product is not effective enough to justify the price so the lag time is acceptable[31].

[i] Cancer survival rates measured in terms of 5-year survival rates. As a result, data on the 5-year survival rate of cancer patients diagnosed in 2019 can only be definitively evaluated after 2024, based on “cohort analysis”. The lack of survival data since 2014 in Europe has recently been described as unsatisfactory[1].

[ii] Whilst this reference could be considered ‘old’, the definition still stands today.

[iii] The Alivia Oncoindex indicates the reimbursement level of oncological drugs in Poland, registered in Europe in the last 15 years and recommended by the European Society of Clinical Oncology (ESMO).