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Adoption of precision health and precision medicine approaches in addressing population health needs in Europe

Final Report

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We hope this report will stimulate further discussion and provide substantive input into the ongoing debate concerning the benefits of precision health and precision medicine in enhancing population health outcomes.

Table of Contents

Executive summary	vi
1. Introduction	1
1.1. Rationale for this report	1
1.2. Definition of key concepts	2
1.2.1. Precision Medicine (PM) and Precision Health (PH)	2
1.2.2. Population health	4
1.2.3. Link between precision medicine (PM), precision health (PH) and population health	4
1.2.4. Population health needs and selection of disease areas	5
1.3. Our approach	6
1.3.1. Development of a review and analysis framework	6
1.3.2. Literature review	7
1.3.3. External interview programme	8
1.3.4. Development of country case studies	8
1.4. The structure of the report	8
2. The use and value of precision health and precision medicine approaches in selected disease areas	9
2.1. Evidence of use and value of precision health (PH) and precision medicine (PM) approaches in selected diseases	9
2.1.1. Cancers	12
2.1.2. Familial hypercholesterolaemia (FH)	21
2.1.3. Type 1 diabetes mellitus (type 1 DM)	27
2.1.4. COVID-19	31
3. Disparities in the adoption of precision health (PH) and precision medicine (PM) approaches across selected countries	38
3.1. Disparities in the adoption of precision health (PH) and precision medicine (PM) approaches for breast and lung cancer in selected countries	38
3.2. Disparities in the adoption of precision health (PH) and precision medicine (PM) approaches for familial hypercholesterolaemia (FH) in selected countries	44
3.3. Disparities in the adoption of precision health (PH) and precision medicine (PM) approaches for type 1 DM in selected countries	49
3.4. Disparities in the adoption of precision health (PH) and precision medicine (PM) approaches for COVID-19 in selected countries	53
4. Conclusions and policy recommendations	56
4.1. Policy recommendations to enhance the use of PH/PM approaches in oncology	56
4.2. Policy recommendations to enhance the use of PH/PM approaches in familial hypercholesterolemia (FH)	57
4.3. Policy recommendations to enhance the use of PH/PM approaches in Type 1 DM	58
4.4. Policy recommendations to enhance the use of PH/PM approaches in COVID-19	59
4.5. General policy recommendations	60
5. Annexes	63

5.1.	Glossary	63
5.2.	Additional information on literature review	65
5.3.	Additional information on external interview programme	66
5.4.	Examples of precision health(PH) and precision medicine (PM) approaches in selected cancer types along patient care pathway	66
5.5.	Examples of precision health (PH) and precision medicine (PM) approaches in FH along patient care pathway	69
5.6.	Examples of precision health (PH) and precision medicine (PM) approaches in type 1 DM along the patient care pathway	71
5.7.	Examples of precision health (PH) and precision medicine (PM) approaches in COVID-19 along the patient care pathway	72
5.8.	Analysis of enablers of faster access to precision cancer therapeutics and diagnostics ..	73

Table of figures

Figure 1:	Visual representation of PH and PM concepts applied in report.....	vii
Figure 2:	Evidence of value of PH/PM along patient pathway in selected disease areas.....	viii
Figure 3:	Enablers of higher levels of adoption of PH/PM innovations	ix
Figure 4:	How PH/PM advances population health needs	5
Figure 5:	Review framework for Precision health(PH)/Precision medicine (PM) value across selected disease areas.....	7
Figure 6:	Three broad applications of PH/PM approaches in population health	9
Figure 7:	Summary of the potential value of PH/PM approaches across the patient journey ...	11
Figure 8:	TTM for HER2 targeted therapies and general oncology medicines	39
Figure 9:	Level of public reimbursement and test order rate for HER2 single biomarker.....	40
Figure 10:	TTM for EGFR targeted therapies and general oncology medicines	40
Figure 11:	Level of public reimbursement level and test order rate for EGFR single biomarker	41
Figure 12:	Enablers of faster access to precision cancer therapeutics and diagnostics	42
Figure 13:	Healthy Years of Life for T1D incidence in selected EU countries.....	52
Figure 14:	Percentage of sequenced new cases of total COVID-19 cases in selected countries	54
Figure 15:	Fold-change in sequencing efficiency (2021/2020) in selected countries.....	54

Table of tables

Table 1:	Global Burden of Diseases, EU (GBD, 2018)*	6
Table 2:	Summary of value of PH/PM across patient care pathway for selected cancers	12
Table 3:	Summary of value of PH/PM across patient care pathway for FH	22
Table 4:	Summary of value of PH/PM across patient care pathway for type 1 DM.....	27
Table 5:	Summary of value of PH/PM across patient care pathway for COVID-19	32
Table 6:	Reimbursement decision dates for selected targeted therapies	38
Table 7:	Comparative analysis of enablers of faster access to innovative cancer medicines...	43

Table 8: Overview of FH screening in selected countries	45
Table 9: Reimbursement and access to continuous glucose monitoring in selected EU countries	50
Table 10: Summary of papers and resources reviewed	65
Table 11: External interviews conducted by CRA	66
Table 12: Some examples of biomarkers for selected cancer types	68

Abbreviations

ABO	ABO blood group system
AI	Artificial intelligence
AML	Acute myeloid leukaemia
BCR-ABL	Breakpoint cluster region Abelson-1
BOADICEA	Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm
CML	Chronic myeloid leukaemia
COSMIC	Catalogue of Somatic Mutations in Cancer
COVID-19	SARS-CoV-2
CRA	Charles River Associates
CVD	Cardiovascular disease
DAISY	Diabetes Autoimmunity Study in the Young
DALY	Disability-adjusted life year
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DSS	Decision support system
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGFR	Epidermal growth factor receptor
EOP	EFPIA Oncology Platform
EU	European Union
ExAC	Exome Aggregation Consortium
FH	Familial hypercholesterolaemia
GBD	Global Burden of Diseases
GENIE	Genomics Evidence Neoplasia Information Exchange
HER2	Human Epidermal Growth Factor Receptor 2
IBIS	International Breast Cancer Intervention Study
ICU	Intensive Care Unit
INCa	Institut National du Cancer (INCa)
LDCT	Low dose computed tomography
LDL	Low density lipoprotein
MODY	Maturity Onset Diabetes of the Young
MRD	Measurable Residual Disease
mRNA	messenger ribonucleic acid
MSI	Microsatellite Instability
MUC1	mucin 1
NCD	Non-communicable disease
NGS	Next-generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic Tyrosine Receptor Kinase
OS	Overall Survival
PCR	Polymerase Chain Reaction
PDT	Precision diagnostic testing
PFS	Progression-free survival
PH	Precision Health
PM	Precision Medicine
QALY	Quality-adjusted life year
QoL	Quality of life
TCGA	The Cancer Genome Atlas
TMB	Tumour Mutation Burden
TTM	Time to market
Type 1 DM	Type 1 diabetes mellitus
UK	United Kingdom
US	United States

Executive summary

The European Federation of Pharmaceutical Industries and Associations (EFPIA), in collaboration with the EFPIA Oncology Platform (EOP), commissioned a report by Charles River Associates (CRA) to highlight the role of precision health (PH) and precision medicine (PM) in addressing population health needs and the benefits they deliver to European health systems.

Rationale for this report

In the last two decades, there has been an acceleration in the development of novel approaches that harness the power of new genome-based technologies, data science and artificial intelligence to address complex medical problems as well as advance the delivery of healthcare solutions. One of the innovative solutions involves precision approaches (PH and PM). The benefits of PM are becoming increasingly apparent in treating specific medical conditions, particularly in cancer and genetic diseases. Beyond these disease areas, a growing body of evidence suggests the efficacy of precision approaches to address population health needs and provide value to many patients with common diseases (including communicable and non-communicable) along the entire care pathway.

PM is often associated with genome-based diagnostics and therapeutics, but in recent times, the use of PM and precision approaches, such as widespread genetic testing, are increasingly becoming more holistic, covering other aspects of the patient care cascade, including disease prevention and patient management. A recent example was population-based viral sequencing in enhancing public health responses during the COVID-19 pandemic. The use of novel data management approaches, such as genetic algorithms in clinical decision support systems for precision patient management, is another example of how precision approaches are being utilised to optimise patient care across many disease areas.

There is a belief that PH and PM not only offer significant hope for individual patients with cancer or rare medical conditions but could also have a transformative impact at the population level. This report explores how carefully considered applications of precision approaches could deliver at population level, mitigating rising healthcare expenditures, particularly in the face of an ageing population with an increase in chronic disease prevalence and the risk of future pandemics.

The distinction between precision medicine and precision health

Precision medicine is defined as a healthcare approach that utilises molecular information (genomic, transcriptomic, proteomic, metabolomic, etc.), phenotypic and health data from patients to generate care insights to prevent or treat human disease resulting in improved health outcomes. ([EFPIA definition](#))

Precision health is a complementary but wider concept that brings into focus determinants of health beyond the provision of medical care and uses extensive population-specific data to provide the right intervention to the right population at the right time. (Khouri et al., 2018)

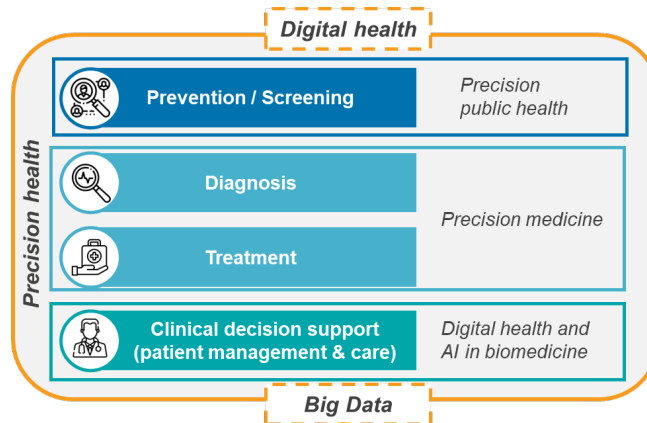
Conceptual framework

The report adopts the concept of PH and PM and develops a framework that utilises precision approaches across the patient care pathway. This approach begins with prevention, where disease screening using precision approaches is deployed to identify

individuals who may be at risk. For diagnosis and treatment, PM can be used to tailor diagnostics and therapies to individual genetic and molecular profiles.

Finally, precision approaches are also used in patient management and care, including the use of clinical decision-support tools to facilitate the delivery of personalised treatment plans (Figure 1).

Figure 1: Visual representation of PH and PM concepts applied in report



Selection of disease areas

While the PH/PM approaches are being used in many disease areas, this report focuses on four disease areas – particular types of cancer (breast and lung), cardiovascular disease (CVD) – familial hypercholesterolemia (FH), type 1 diabetes mellitus (DM) and infectious disease (COVID-19).

These disease areas were selected based on their contribution to the disease burden in Europe according to the Global Burden of Diseases (GBD). The objective is to look beyond rare conditions for a small patient population, selecting disease areas that help ascertain how PH/PM approaches are useful in addressing population health needs for common medical conditions. Furthermore, the selection of FH, type 1 DM and COVID-19, in particular, helps to examine the utility of PH and PM beyond diagnosis and treatment in oncology, the domain where PM's role has been most frequently examined.

Summary of findings

Our analysis evaluated the value of PH and PM in selected disease areas by assessing nine dimensions of value that cover the patient care pathway, as shown in Figure 2.

There is evidence of the significant value of PH and PM in cancer, specifically in the diagnosis and treatment phases. The development of companion diagnostics (devices which are essential for the safe and effective use of a corresponding medicinal product), including next-generation sequencing, provides clinicians with more precise tools for identifying patients likely to benefit from targeted therapies.

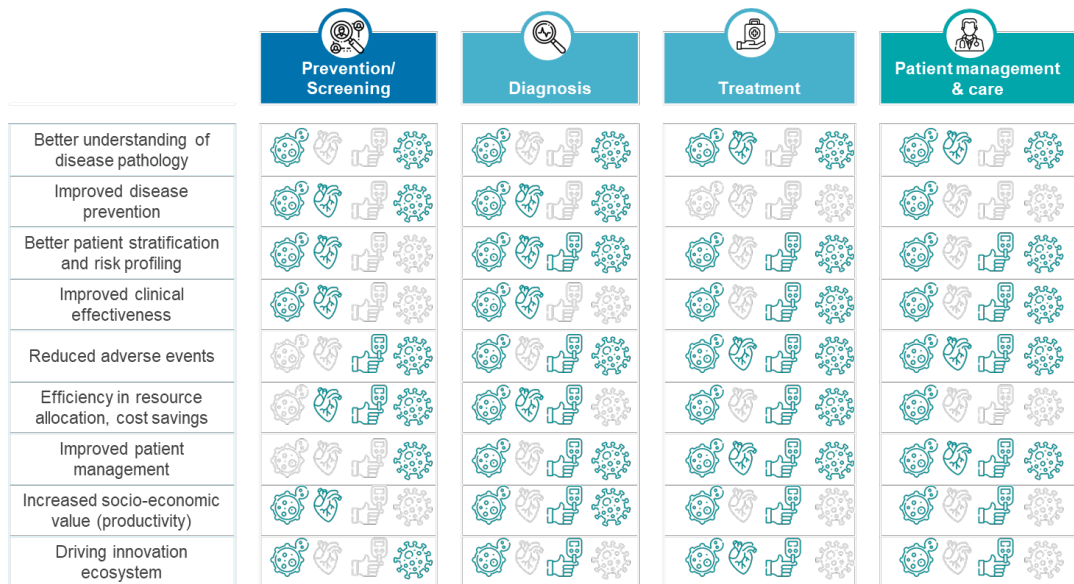
For FH, the primary value of PH and PM is in screening and diagnosis, which involves genetic testing to confirm the diagnosis and tailor patient care and management to prevent premature cardiovascular events.

In the case of type 1 DM, the primary value of PH and PM approaches is in patient management and care, specifically through the use of continuous glucose monitoring (CGM).

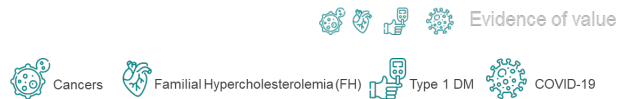
For COVID-19, the most significant value of PH and PM is in prevention. The use of population-based viral genomic sequencing enables more effective disease surveillance and the development of vaccines that target specific mutations present in different strains of the virus.

The summary of key evidence of the value of PH and PM for each disease area are presented in Figure 2.

Figure 2: Evidence of value of PH/PM along patient pathway in selected disease areas



Source: CRA analysis



In addition to examining evidence of the value of precision approaches, we also analysed the level of adoption of PH and PM approaches across selected EU countries (Denmark, Estonia, France, Germany, Poland, Spain) and England. The report provides insights into the disparities in the adoption of precision approaches and highlights areas for improvement.

Disparities in the adoption of precision approaches

1 - Disparities in the adoption of PH/PM approaches for oncology in selected countries

Since the adoption of any health technology typically requires market access authorisation and agreement to reimburse, our analysis of the level of adoption of PH/PM approaches for oncology-focused on identifying country differences in average time to availability or time to market (TTM) for newly approved precision cancer therapeutics (between 2017 and 2021). For the analysis, we selected recently approved targeted therapies for HER2 breast cancer and EGFR non-small cell lung cancer in the last five years. In addition, we assessed the availability and use of companion diagnostics needed to apply selected targeted therapies.

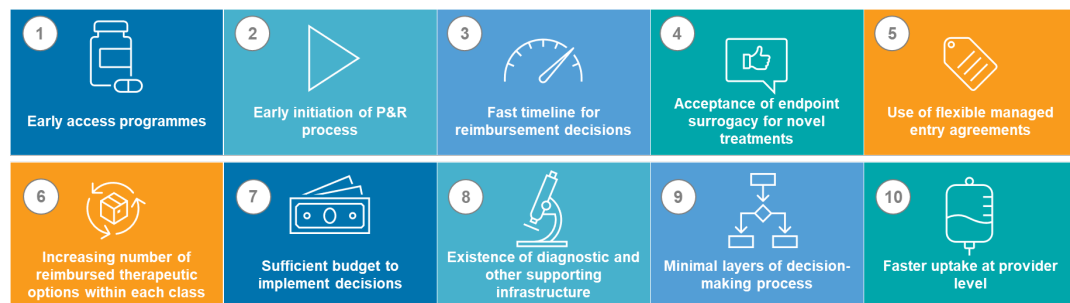
Based on the analysis, we found notable differences in the adoption of recent PH/PM innovations in cancer diagnosis and treatment across selected countries. The average TTM for newer HER2 targeted therapies (504 days) is generally longer than that of all oncology medicines, including HER2 therapies and other precision medicines (393 days). A similar

trend was found for average TTM for EGFR therapies (469 days) also longer than that of all oncology medicines, including EGFR therapies and other precision medicines. This trend suggests longer access delays to recent PH/PM innovations in cancer care across selected countries.

While the level of public reimbursement for HER2 and EGFR companion diagnostics is relatively high across all countries, the test order rate (number of tests conducted) is much lower for EGFR than for HER2.

Lastly, our analysis identified ten good practices that serve as enablers of faster access and higher levels of adoption of PH/PM innovations (Figure 3).

Figure 3: Enablers of higher levels of adoption of PH/PM innovations



Source: *The root causes of unavailability and delay to innovative medicines (CRA/EFPIA 2022)* and *Improving time to patient access to innovative oncology therapies in Europe (Vintura 2020)*

Every day of avoidable access delay to PH/PM innovations in cancer care adds to years of potential life lost and a missed opportunity to address population health needs, especially for cancers with the highest burden.

Specific policy recommendations to enhance the use of PH/PM approaches in oncology are provided in Chapter 4.1.

2 - Disparities in the adoption of PH/PM approaches for FH in selected countries

FH is a genetic disorder that often goes undiagnosed, with a significant proportion of affected individuals in Europe remaining unaware of their condition. While it may be argued that only a relatively small subset of patients suffering from CVD have an underlying diagnosis of FH, it is estimated that there are about 2.5 million Europeans affected with FH, and only 6-10% of those with FH are actually diagnosed.

Despite genetic testing for FH being available and covered by health systems in most selected countries, the challenge of identifying suitable candidates for such testing is significant. This is reflected in the low to medium-range utilisation rates (defined using the number of identified FH cases in the country) observed in all the selected countries. However, England and Germany's implementation of pilot paediatric screening programs and innovative approaches to FH genetic testing and cascade screening serve as best practice examples. By analysing these case studies, we gained insights into the considerable potential that PH/PM approaches can offer. Although progress has been made in some countries, widespread FH screening for children and precision medicine approaches are still in their nascent stages.

Specific policy recommendations to enhance the use of PH/PM approaches in FH are provided in Chapter 4.2.

3 – Disparities in the adoption of PH/PM approaches for Type 1 DM in selected countries

The impact of PH/PM in the clinical decision support or management of type 1 DM has been of great interest to healthcare professionals, researchers, and patients. All selected EU countries provide access to continuous glucose monitoring (CGM) for type 1 DM patients, and it is fully reimbursed in all except Poland (reimbursed 70%). The main differences in access are linked to eligible populations with significant variations of a target population in selected countries. Age limits also limit access to CGM in Denmark, Estonia, and Poland. Countries with broader access, such as Germany, England, and France, mostly had higher currently healthy years of life and lower potential healthy years restored.

The next milestone in innovation will be the widespread use of closed-loop insulin delivery systems in combination with CGM, which would allow each patient to monitor glucose levels and adjust insulin levels using subcutaneous insulin pumps and the input of advanced algorithms, thereby tailoring treatment to each patient's needs and profile. With these advancements, patient outcomes are likely to improve further.

Specific policy recommendations to enhance the use of PH/PM approaches in type 1 DM are provided in Chapter 4.3.

4 - Disparities in the adoption of PM/PH approaches for COVID-19 in selected countries

The COVID-19 pandemic has highlighted the significance of PH/PM approaches in prevention strategies, with the global SARS-CoV-2 genomic surveillance playing a pivotal role in this regard. A comprehensive evaluation of the sequencing intensity and efficiency of SARS-CoV-2 across selected countries and its potential impact on public health was conducted. Sequences shared via the Global Initiative on Sharing All Influenza Data (GISAID) platform were analyzed to estimate the sequencing intensity and sequencing efficiency across selected countries.

The findings revealed heterogeneity in the availability of SARS-CoV-2 genomic surveillance and sequencing among different countries, with some countries exhibiting a higher frequency of routine genomic surveillance. This led to a higher percentage of sequenced COVID-19 cases in these countries, which could have enhanced their prevention policies and strategies. Notably, the United Kingdom and Denmark were among the first countries to implement widespread genomic sequencing of COVID-19 samples, utilising this information to inform decisions on social distancing measures, border control, and vaccine strategy. The identification of new and highly transmissible virus variants facilitated the implementation of additional measures, including travel restrictions and lockdowns, to curb the spread of these variants and protect public health. In contrast, some countries, such as Spain and Poland, lagged behind in sequencing, making it challenging to effectively implement targeted public health measures, track variants, and perform contact tracing.

The COVID-19 pandemic has underscored the importance of establishing a robust sequencing infrastructure for effective public health response. Many European countries have leveraged advancements in genomic sequencing for screening and prevention during the pandemic, with the necessary infrastructure built to mitigate the risks of potential future diseases. Sequencing is a powerful tool that can improve precision, efficacy, and efficiency in public health response.

Specific policy recommendations to enhance the use of PH/PM approaches in COVID-19 are provided in Chapter 4.4.

General policy recommendations to enhance the adoption of PH/PM approaches in addressing population healthcare needs across Europe

PH/PM has the potential to greatly improve population health outcomes in Europe through better prevention, screening, diagnosis, treatment and patient management. However, for PH/PM to deliver for European patients, several key policy recommendations must be implemented.

- ***Prioritising availability and investment in PH/PM technologies:*** Investing in PH/PM technologies like genomic sequencing and targeted therapies can ensure that patients have access to the most advanced and beneficial health technologies, leading to better prevention, screening, diagnosis, treatment, and patient management. By ensuring availability and investment in these technologies, Europe can remain a leader in healthcare innovation, which can help address population health needs. This is important for all disease areas considered in this report. We find that PH/PM technologies can improve patient outcomes, increase efficiency in healthcare delivery, and lead to better resource allocation, which can significantly impact the overall sustainability and effectiveness of the healthcare system.
- ***Data sharing and collaboration:*** Prioritising data sharing and collaboration among healthcare providers, researchers, and patients can build a robust data ecosystem that supports the development and implementation of PH/PM approaches, providing a more comprehensive understanding of population health needs. Data sharing was particularly important during the COVID-19 pandemic, but it is also important for cancer and type-1 DM research. By leveraging initiatives like the European Healthcare Data Space (EHDS) to establish strong data governance frameworks and define interoperability standards, Europe can improve disease prevention and management and promote medical research, ultimately improving population health outcomes.
- ***Education and training of healthcare providers:*** By prioritising education and training for healthcare providers on PH/PM approaches, including interpretation of genomic data and the use of advanced technologies like machine learning and artificial intelligence, Europe can ensure that healthcare providers have the necessary skills and knowledge to address population healthcare needs. For cancers, it is important that healthcare providers are educated on the benefits of PH/PM approaches. Europe's Beating Cancer Plan can be leveraged to develop and implement training programs for healthcare providers, specifically focused on PH/PM approaches. For FH and type 1 DM, improved education will help identify and diagnose patients and implement PH/PM approaches to treatment and management. Raised awareness of the general public and healthcare providers on the benefits of genomic sequencing during COVID-19 could have a spillover effect in other disease areas.
- ***Ensure equal access to PH/PM approaches:*** It is crucial to ensure that all patients have access to the best possible care through PH/PM approaches, including targeted therapies and diagnostics, without any inequalities in patient access to medicines and diagnostics across Europe. To achieve this, pricing and reimbursement (P&R) policies must be aligned with the value delivered by

innovations. In addition, P&R policies should evolve to reflect advances in precision approaches. A disconnect between therapy reimbursement and of their companion diagnostics also contributes to patient access delays. Hence P&R policies should also seek to address this challenge. By prioritising value-based P&R policies with minimal or no time delay between market authorisation and reimbursement decision, patients could have timely access to PH/PM interventions, thereby contributing to improvement in population health outcomes across Europe. In the report, we observed inequalities in cancer care regarding access to targeted therapies, precision diagnostics, and access to continuous glucose monitoring (CGM) in type 1 DM.

- **Patient-centred care plans:** Developing patient-centred care plans tailored to individual needs and circumstances through PH/PM approaches can promote individualized and more effective treatments, ultimately contributing to the overall improvement of population health outcomes. The report finds that PH/PM approaches are integral to establishing patient-centred care plans, especially in cancers and type 1 DM, as precision approaches provide value along the whole patient care pathway in these diseases. By utilising data sharing and collaboration among healthcare providers, researchers, and patients, Europe can develop patient-centred care plans that take into account a patient's unique genetic and environmental factors, leading to more effective treatment outcomes and improved allocation of health resources.
- **Building infrastructure and raising awareness:** Building infrastructure for PH/PM approaches like genetic testing and genomic sequencing and raising awareness of the benefits of these approaches in disease prevention and surveillance can improve disease prevention and detection before symptoms appear, ultimately improving population health outcomes. By prioritising building a robust infrastructure for PH/PM approaches and raising awareness of the benefits of these approaches in disease prevention and surveillance, Europe can encourage greater uptake and use of these approaches.

By embracing these policy recommendations, Europe has the opportunity to establish itself as a leader in the advancement and application of PH/PM approaches to address the complex healthcare requirements of populations at large. Integral to this effort is the establishment of a robust data infrastructure, the promotion of data sharing, and the development of digital tools. These elements are crucial enablers of PH/PM, and they are fundamental to enhancing the efficiency, equity, health outcomes, value-for-money, and financial sustainability of health systems. With a focus on preventive measures, diagnosis, treatment strategies, and patient management techniques, Europe can elevate the standard of healthcare delivery and achieve substantial improvements in the health outcomes of its citizens.

1. Introduction

The European Federation of Pharmaceutical Industries and Associations (EFPIA), in collaboration with the EFPIA Oncology Platform (EOP), commissioned Charles River Associates (CRA) to help develop a report that highlights the role precision health (PH) and precision medicine (PM) play in addressing population health needs and the benefits these deliver to European health systems.

1.1. Rationale for this report

This report highlights areas where policymakers, healthcare providers, patients and industry can work together to enhance the use of precision medicine. In the last two decades, there has been an acceleration in the development of novel approaches that harness the power of new technologies and data science to address complex medical problems as well as advance the delivery of healthcare solutions. One of such novel solutions is precision approaches (PH and PM), defined below in 1.2.1. Using precision approaches, more effective treatments and fewer side effects can potentially improve outcomes for patients with different types of diseases and reduce the overall burden on health systems. Also, the ability to identify patients at risk of disease allows health systems to focus on prevention rather than cure.

The benefits of precision medicine are becoming increasingly apparent in treating specific medical conditions, particularly in cancer and genetic diseases. Despite some scepticism about the efficacy of precision medicine in benefiting larger population groups or improving public health for common diseases^{1,2}, a growing body of evidence suggests otherwise. There is a belief that PH and PM not only offer significant hope for individual patients but could also have a transformative impact at the population level.

Building on a recent body of evidence, it is important for European health systems to leverage the revolutionary impact of precision approaches to address population health needs and provide value to many patients with common diseases along the entire care pathway, not only in cancer or rare diseases.

Precision medicine is often regarded as synonymous with orphan drugs or strictly with targeted oncology medicines. This can lead to a misconception that, at best, PH/PM is peripheral to population health, or at worst, because it deals with high-cost interventions for very small numbers of people, it is detrimental to population health as a whole.

Precision medicine (and precision health) is, however, a much broader concept, which includes targeted treatments for rare diseases but is not limited to them. Rather, it has implications for the population as a whole, and is therefore central to any discussion of population health and health system value.

In the report, we explore how precision medicine approaches could mitigate rising healthcare expenditures in the face of challenges like an ageing population with the surge of chronic diseases and in the case of pandemics. It is hoped that this report will help

1 Joyner, M. J., & Paneth, N. (2015). Seven Questions for Personalized Medicine. *JAMA*, 314(10), 999–1000. <https://doi.org/10.1001/jama.2015.7725>

2 Khoury, M. J., & Galea, S. (2016). Will Precision Medicine Improve Population Health?. *JAMA*, 316(13), 1357–1358. <https://doi.org/10.1001/jama.2016.12260>

galvanise necessary action towards a shared vision of equitable access to precision approaches across healthcare systems in Europe.

1.2. Definition of key concepts

As this report aims to highlight the role and value of precision approaches in addressing population health needs, several key concepts, including PH and PM, need to be defined.

1.2.1. Precision Medicine (PM) and Precision Health (PH)

Precision medicine (PM) – This report uses the EFPIA definition of PM, which is *a healthcare approach that utilises molecular information (genomic, transcriptomic, proteomic, metabolomic, etc), phenotypic and health data from patients to generate care insights to prevent or treat human disease resulting in improved health outcomes.*³ Compared to other definitions, this provides a broad view of what PM entails, not limited to diagnostics and therapeutics but also disease prevention. The definition further highlights a variety of data sources – molecular, phenotypic and other health data – that drive PM interventions.

Personalised medicine is sometimes used interchangeably with precision medicine (PM) but are not necessarily synonymous.^{4,5,6,7} In 2015, the Council of the European Union defined personalised medicine 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.*⁸

Based on these definitions, personalised medicine appears to mainly focus on tailoring medical care (prevention, diagnosis and treatments) to individual patient needs based on available evidence and consideration of circumstances and clinical resources, while PM is concerned with how medical approaches can be developed based on the combination of

3 Precision medicine. (n.d.). Retrieved September 28, 2022, from <https://www.efpia.eu/about-medicines/development-of-medicines/precision-medicine/>

4 McAlister, F. A., Laupacis, A., & Armstrong, P. W. (2017). Finding the right balance between precision medicine and personalized care. *CMAJ: Canadian Medical Association journal*, 189(33), E1065–E1068. <https://doi.org/10.1503/cmaj.170107>

5 Iriart J. (2019). Precision medicine/personalized medicine: a critical analysis of movements in the transformation of biomedicine in the early 21st century. *Public health notebooks*, 35(3), e00153118. <https://doi.org/10.1590/0102-311X00153118>

6 MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). What is the difference between precision medicine and personalized medicine? What about pharmacogenomics? [updated 2022 May 17; [about 8 p.]. Available from: <https://medlineplus.gov/genetics/understanding/precisionmedicine/precisionvspersonalized/>

7 National Research Council (US) Committee on A Framework for Developing a New Taxonomy of Disease. (2011). *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*. National Academies Press (US).

8 The Council of the European Union (2015). Council conclusions on personalised medicine for patients (2015/C 421/03). Available at: [https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52015XG1217\(01\)&from=FR#:~:text=However%2C%20it%20is%20widely%20understood,and%20for%20to%20determine%20the](https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52015XG1217(01)&from=FR#:~:text=However%2C%20it%20is%20widely%20understood,and%20for%20to%20determine%20the)

genetic, environmental, and social factors, which could be tailored to groups of individuals.⁹
10, 11, 12, 13, 14, 15, 16

Precision health (PH) – This is a complementary but wider concept to PM. Precision Medicine is a part of PH. Precision health brings into focus determinants of health beyond the provision of medical care and uses extensive population-specific data to provide the right *intervention* to the right population at the right time.^{17, 18} In addition to the use of data from health (clinical) records, PH utilises other forms of data, including omics data¹⁹ and data from lifestyle, environmental and social determinants of health (education, income, housing etc.) to tailor interventions to improve population health outcomes.^{20, 21} PH places greater emphasis on health promotion and disease prevention (sometimes referred to as

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- 9 McAlister, F. A., Laupacis, A., & Armstrong, P. W. (2017). Finding the right balance between precision medicine and personalized care. *CMAJ: Canadian Medical Association journal*, 189(33), E1065–E1068. <https://doi.org/10.1503/cmaj.170107>
- 10 EFPIA. Precision Medicine: Giving the right medicine, to the right patient, at the right time, available at: <https://www.efpia.eu/about-medicines/development-of-medicines/precision-medicine/>
- 11 The Horizon 2020 Advisory Group, cited by the EU Commission, What personalised medicine means, available at: https://research-and-innovation.ec.europa.eu/research-area/health/personalised-medicine_en#:~:text=Although%20there%20is%20no%20universally,therapeutic%20strategy%20for%20the%20right
- 12 Personalised Medicine Coalition. Personalised Medicine Factsheet, available at: https://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/pmc_age_of_pmc_factsheet.pdf
- 13 National Cancer Institute. Personalized medicine, available at: <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/personalized-medicine>
- 14 NHS England. Personalised medicine, available at: <https://www.england.nhs.uk/healthcare-science/personalisedmedicine/>
- 15 National Research Council (US) Committee on A Framework for Developing a New Taxonomy of Disease. (2011). *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*. National Academies Press (US).
- 16 Personalised medicine. (n.d.). Retrieved October 10, 2022, from https://research-and-innovation.ec.europa.eu/research-area/health/personalised-medicine_en
- 17 Khoury, M. J., Engelgau, M., Chambers, D. A., & Mensah, G. A. (2018). Beyond Public Health Genomics: Can Big Data and Predictive Analytics Deliver Precision Public Health?. *Public health genomics*, 21(5-6), 244–250. <https://doi.org/10.1159/000501465>.
- 18 Velmovitsky, P. E., Bevilacqua, T., Alencar, P., Cowan, D., & Morita, P. P. (2021). Convergence of Precision Medicine and Public Health Into Precision Public Health: Toward a Big Data
- 19 Omic data include genetic and genomic sequence, protein, metabolite, and microbiome information
- 20 Minor, L. and Rees, M. (2020). Introduction: The Power of Precision Health. In *Discovering Precision Health* (eds L. Minor and M. Rees). <https://doi.org/10.1002/9781119672715.ch0>
- 21 Khoury, M. J., Iademarco, M. F., & Riley, W. T. (2016). Precision Public Health for the Era of Precision Medicine. *American Journal of Preventive Medicine*, 50(3), 398–401. <https://doi.org/10.1016/j.amepre.2015.08.031>

precision public health). It leverages advances in device technology and data science.^{22,23,24,25}

The use of a variety of data sources to inform PH approaches aligns with EFPIA's definition of PM. As the view of EFPIA regarding precision approaches offers a broader view and linkage with population health, this report focuses on precision health and precision medicine and their link with population health.

1.2.2. Population health

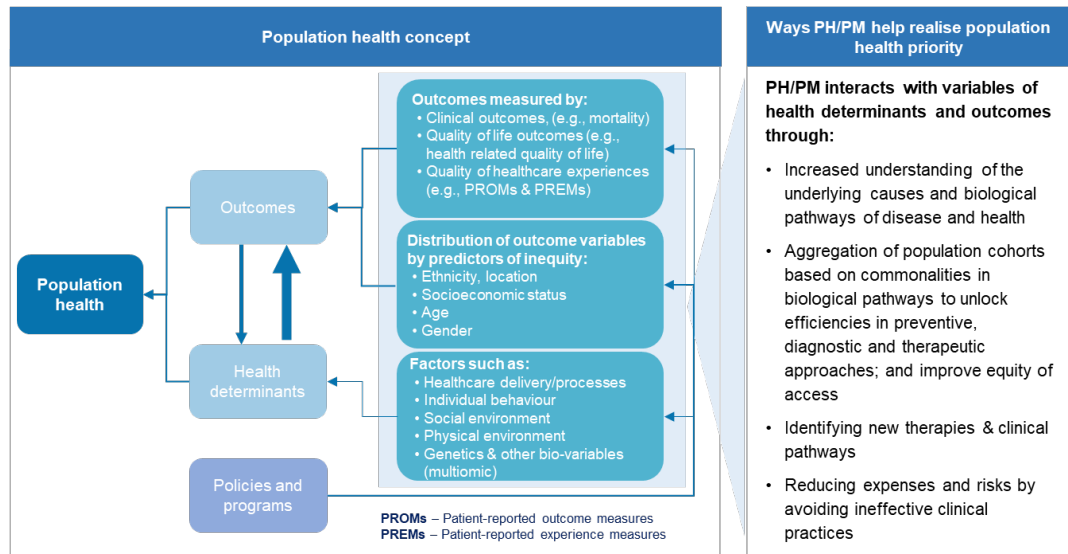
According to Kindig et al. (2003), population health as a concept of health is defined as *the health outcomes of a group of individuals, including the distribution of such outcomes within the group, and aims to improve the health of an entire human population*. A key priority is reducing health inequities or disparities among different population groups, which represents a change in the focus from an individual level to a population-based level.^{26,27} So the focus is on larger populations in society. Although there is no formal definition of how large a group needs to be to qualify as population health, we have focused on the largest population adopting PH and PM approaches, thus counteracting the notion of PM being a solution only for a few, whereas it is a solution for the many at the population level.

1.2.3. Link between precision medicine (PM), precision health (PH) and population health

According to the literature, the concept of PH/PM, as defined, could play a critical role in advancing the population health objective of reducing health disparities among different population groups. PH/PM helps to *"better understand underlying causes and biological pathways of disease and health and how population cohorts can be aggregated based on commonalities in biological pathways to unlock efficiencies in preventive, diagnostic and therapeutic approaches; and improve equity of access."*^{28,29}

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- 22 Minor, L. and Rees, M. (2020). Introduction: The Power of Precision Health. In *Discovering Precision Health* (eds L. Minor and M. Rees). <https://doi.org/10.1002/9781119672715.ch0>
- 23 Weeramanthri TS, Dawkins HJS, Baynam G, Bellgard M, Gudes O, Semmens JB. Editorial: precision public health. *Front Public Health*. (2018) 6:121. [10.3389/fpubh.2018.00121](https://doi.org/10.3389/fpubh.2018.00121)
- 24 Minor, L. and Rees, M. (2020). Introduction: The Power of Precision Health. In *Discovering Precision Health* (eds L. Minor and M. Rees). <https://doi.org/10.1002/9781119672715.ch0>
- 25 Khoury, M. J., Iademarco, M. F., & Riley, W. T. (2016). Precision Public Health for the Era of Precision Medicine. *American Journal of Preventive Medicine*, 50(3), 398–401. <https://doi.org/10.1016/j.amepre.2015.08.031>
- 26 Kindig, D., & Stoddart, G. (2003). What is population health?. *American journal of public health*, 93(3), 380–383. <https://doi.org/10.2105/ajph.93.3.380>
- 27 Optimizing Precision Medicine for Public Health: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6416195/>
- 28 Bilkey, G. A., Burns, B. L., Coles, E. P., Mahede, T., Baynam, G., & Nowak, K. J. (2019). Optimizing Precision Medicine for Public Health. *Frontiers in public health*, 7, 42. <https://doi.org/10.3389/fpubh.2019.00042>
- 29 What Is Population Health? (n.d.). Improving Population Health. Retrieved September 28, 2022, from <https://www.improvingpopulationhealth.org/blog/what-is-population-health.html>

Figure 4: How PH/PM advances population health needs



Source: Adapted from Kindig et al. (2003) and Burns et al. (2019)

Figure 4 shows the key elements of population health (i.e., variables of health determinants and outcomes) and ways in which precision approaches could influence these variables to realise population health priority. The link between PH/PM and population health is not only about genes, medicines and diseases but also involves gaining a deeper understanding into complex life course interactions between biological factors with a range of personal, environmental and social determinants of health. This understanding can help track disease occurrence in communities and population groups and inform the design and implementation of effective interventions that can benefit all segments of the population.^{30,31,32,33}

1.2.4. Population health needs and selection of disease areas

To determine what constitutes population health needs, we consulted the Global Burden of Diseases (GBD) to help identify which diseases contribute the most burden in terms of mortality and morbidity (measured in disability-adjusted life years) in Europe.³⁴ Based on the definition of population health, we selected four disease areas, including specific types

30 National Research Council (US) Committee on A Framework for Developing a New Taxonomy of Disease. (2011). *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*. National Academies Press (US).

31 Weeramanthri, T. S., Dawkins, H. J. S., Baynam, G., Bellgard, M., Gudes, O., & Semmens, J. B. (2018). Editorial: Precision Public Health. *Frontiers in Public Health*, 6. <https://www.frontiersin.org/articles/10.3389/fpubh.2018.00121>








32 Velmovitsky, P. E., Bevilacqua, T., Alencar, P., Cowan, D., & Morita, P. P. (2021). Convergence of Precision Medicine and Public Health Into Precision Public Health: Toward a Big Data Perspective. *Frontiers in Public Health*, 9. <https://www.frontiersin.org/articles/10.3389/fpubh.2021.561873>

33 Minor, L. and Rees, M. (2020). Introduction: The Power of Precision Health. In *Discovering Precision Health* (eds L. Minor and M. Rees). <https://doi.org/10.1002/9781119672715.ch0>

34 Deaths and disability-adjusted life years within the EU in 2017 from non-communicable diseases | Knowledge for policy. (n.d.). Retrieved September 28, 2022, from https://knowledge4policy.ec.europa.eu/health-promotion-knowledge-gateway/eu-burden-non-communicable-diseases-key-risk-factors-1_en

of cancer (breast and lung), cardiovascular diseases (FH), chronic respiratory diseases and type 1 diabetes mellitus, and reviewed if PH/PM approaches were being applied. Table 1 shows the ranking of disease burden in Europe according to GBD (2018).

Table 1: Global Burden of Diseases, EU (GBD, 2018)*

Disease	% Contribution to total burden in the EU	
	Deaths	DALYs**
Non-communicable diseases (NCDs)	91.3	86.6
 Cardiovascular diseases (CVDs)	36.4	18.4
 Cancers	27.6	18.6
 Neurological disorders	11.5	8.5
 Chronic respiratory diseases	5.0	4.5
 Digestive diseases	4.6	4.1
 Diabetes & kidney diseases	3.7	4.3
... Other NCDs	1.3	3.8
 Communicable diseases	8.7	13.4

*as of 2020, COVID-19 may have distorted the ranking of the global burden of diseases

** Disability-adjusted life years

1.3. Our approach

To examine the benefits of PH/PM and how it addresses population health needs, we adopted a four-step methodology:

- Development of a review and analysis framework
- Literature review
- An external interview programme
- Development of country case studies

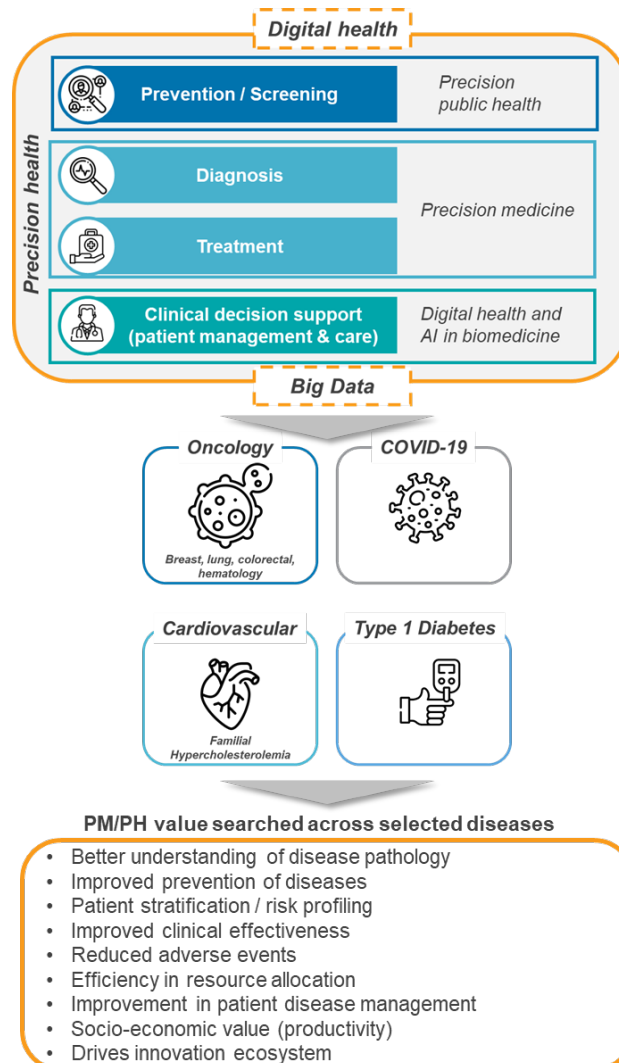
1.3.1. Development of a review and analysis framework

The first step was to develop a framework, as shown in Figure 5, to help organise the literature review and analysis of findings. The framework incorporates precision approaches along the patient care pathway, starting from prevention (identification of risk factors and genetic predisposition before pathology develops) to diagnosis and treatment (involving precision diagnosis and medicines) and patient management/care, including the use of clinical decision support to facilitate delivery of precision approaches. The framework also entails the role of PH/PM enablers, including big data³⁵ and digital tools, in driving precision approaches. In the review framework, predefined categories of the value of PH/PM³⁶ are used to highlight the benefits of PH/PM along the patient care pathway found in the literature.

35 EMA, 'Big data' is a widely-used term without a commonly-accepted definition. The HMA/EMA Big Data Task Force defined big data as 'extremely large datasets which may be complex, multi-dimensional, unstructured and heterogeneous, which are accumulating rapidly and which may be analysed computationally to reveal patterns, trends, and associations. In general, big data sets require advanced or specialised methods to provide an answer within reliable constraints', available at <https://www.ema.europa.eu/en/about-us/how-we-work/big-data>

36 Wilsdon, T., Barron, A., Edwards, G. & Lawlor Charles River Associates, R. The benefits of personalised medicine to patients, society and healthcare systems Final Report. (2018)

Figure 5: Review framework for Precision health(PH)/Precision medicine (PM) value across selected disease areas



Source: CRA

1.3.2. Literature review

In the past five years, there has been a focused effort to explore the potential benefits and limitations of precision approaches in healthcare. This effort has involved the development of an evidence base and compelling arguments in support of precision medicine, as well as the identification of challenges around its availability and wider application within health systems. In addition, the associated policy issues have been explored to better understand the implications of precision medicine for healthcare stakeholders. CRA conducted a targeted literature review on the definition of PH/PM and its value, link with population health and existing PH/PM approaches across selected disease areas. While the review was not a systematic review, the focus was to identify available evidence of the value of precision approaches in published literature. Data sources are a mix of primary studies, reviews and expert opinions. Further details of the literature review process are provided in Annex 5.2.

1.3.3. External interview programme

As a complement to our research, we conducted an external interview program to validate our review and analysis framework, key findings from the literature review and case studies. The purpose of the interviews was to gather additional insights and perspectives from a variety of stakeholder groups across different countries. CRA conducted eight expert interviews with a range of stakeholders, including academics, healthcare professionals, and representatives from patient organizations, and independent experts in precision medicine. During these interviews, we discussed the case studies in detail, confirmed our findings, and received valuable feedback from the experts. We also had the opportunity to discuss policy recommendations and gain a deeper understanding of the challenges and opportunities for improving access and adoption of PM approaches in Europe. The expert interviews provided valuable insights that helped to further inform our research and conclusions.³⁷

1.3.4. Development of country case studies

In our analysis, we have chosen to focus on country case studies to showcase the current state of adoption and access to PH/PM approaches in Europe across four diseases. The goal of this analysis is to provide a comprehensive understanding of the level of access and availability of PH/PM approaches for improving population health outcomes. The selection of case studies was based on a careful review of the literature and expert opinion, where PH/PM was deemed to have the greatest potential to address population health needs. Regarding geographical spread and availability of information on the adoption of PH/PM approaches, the countries include Denmark, England, Estonia, France, Germany, Poland and Spain. In Chapter 2, we delve deeper into each selected disease area and provide a rationale for the metrics we have chosen to use in our analysis.

1.4. The structure of the report

The structure of this report is as follows:

- **Chapter 2** examines existing evidence of the use and value of PH/PM in the four diseases-specific types of cancer, cardiovascular diseases (FH), type 1 diabetes mellitus and COVID-19 along patient pathways (prevention, diagnosis, treatment and patient management).
- **Chapter 3** highlights our analysis of levels of adoption of PH/PM approaches using pre-selected metrics in countries of focus.
- **Chapter 4** presents our conclusions and sets policy options for ensuring access and availability of PH/PM approaches in Europe.

2. The use and value of precision health and precision medicine approaches in selected disease areas

Based on the definition of population health needs mentioned in section 1 of the report, we selected four disease areas, including specific types of cancer, cardiovascular disease, type 1 diabetes mellitus and COVID-19, and reviewed based on whether PH/PM approaches were being applied.

2.1. Evidence of use and value of precision health (PH) and precision medicine (PM) approaches in selected diseases

Using the review framework, we found PH/PM approaches already play a critical role in addressing population health needs in selected disease areas. There are three broad categories where PH/PM approaches are currently being used in population health (Figure 6).

Figure 6: Three broad applications of PH/PM approaches in population health



The first is the linkage of various health data and precision technologies to measurable outcomes in subpopulations stratified by persons, place, and time.³⁸ An example is precision risk stratification using age and polygenic risk score in stratifying women into risk categories for breast cancer screening rather than using age alone.³⁹ The second is the development of gene-based approaches to health by implementing genomic interventions such as the use of biomarkers and genome-wide sequencing to prevent, investigate, treat and manage diseases.^{40,41,42,43} The third is the application of emerging technologies (data and digital) for measuring disease, pathogens, exposures, behaviours, and susceptibility

- 38 Khoury, M. J., & Galea, S. (2016). Will Precision Medicine Improve Population Health? *JAMA*, 316(13), 1357–1358. <https://doi.org/10.1001/jama.2016.12260>
- 39 Narod, S. A. (2018). Personalised medicine and population health: Breast and ovarian cancer. *Human Genetics*, 137(10), 769–778. <https://doi.org/10.1007/s00439-018-1944-6>
- 40 HealthManagement.org. (n.d.). Radiology Management, ICU Management, Healthcare IT, Cardiology Management, Executive Management. HealthManagement. Retrieved October 10, 2022, from <https://healthmanagement.org/c/hospital/issuearticle/precision-health-and-population-health-can-they-intersect-effectively>
- 41 Grossman, D. C., Larson, E. B., & Sox, H. C. (2020). Integrating Personalized Medicine With Population Health Management: The Path Forward. *JAMA*, 324(7), 631–632. <https://doi.org/10.1001/jama.2020.1406>
- 42 Loeber, J. G., Platis, D., Zetterström, R. H., Almashanu, S., Boemer, F., Bonham, J. R., Borde, P., Brincat, I., Cheillan, D., Dekkers, E., Dimitrov, D., Fingerhut, R., Franzson, L., Grosej, U., Hougaard, D., Knapkova, M., Kocova, M., Kotori, V., Kozich, V., ... Schielen, P. C. J. I. (2021). Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010. *International Journal of Neonatal Screening*, 7(1), 15. <https://doi.org/10.3390/ijns7010015>
- 43 Salisbury, F. (n.d.). Precision Medicine: The next revolution in healthcare. Retrieved October 10, 2022, from <https://www.mewburn.com/news-insights/precision-medicine>

in populations to improve the ability to prevent disease, promote health, and reduce health disparities in populations.^{44,45}

In this report, we identified nine main dimensions of value that might be contributed by PH/PM along the patient care pathway, which include:

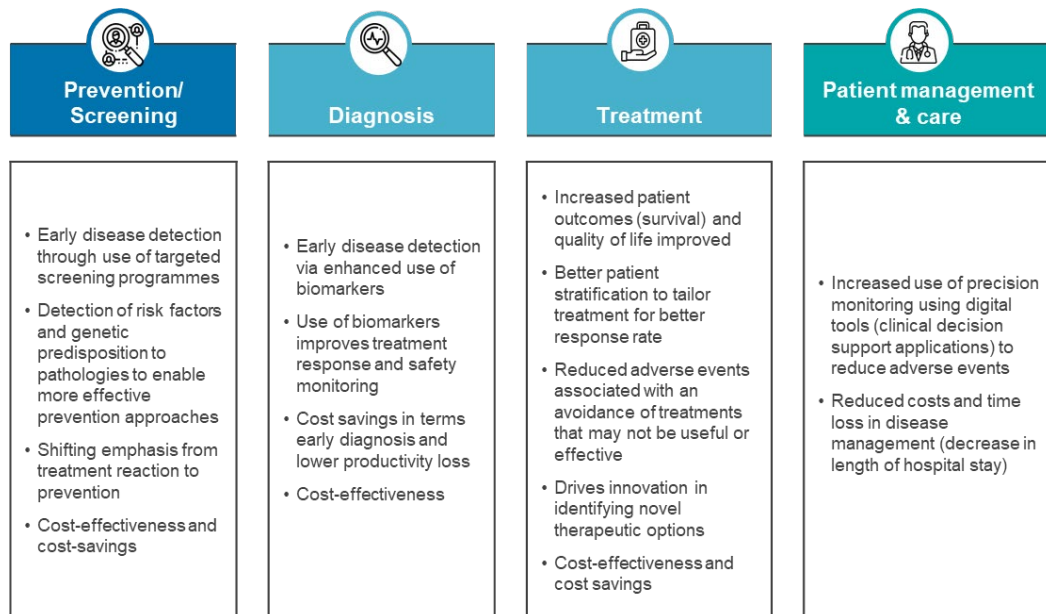
- i. better understanding of disease pathology
- ii. improved disease prevention
- iii. better patient stratification and risk profiling
- iv. improved clinical effectiveness
- v. reduced adverse events
- vi. efficiency in resource allocation, cost savings and cost-effectiveness
- vii. improved patient management
- viii. increased socio-economic value (productivity) and
- ix. driving innovation ecosystem.

The report includes a visual representation in Figure 7, demonstrating how the nine dimensions of value can be applied throughout the patient care pathway to enhance the overall value of precision medicine approaches. By depicting how these benefits can be achieved and experienced by patients at different stages of their care journey, Figure 7 serves as a useful tool for understanding the potential impact of precision health on patient outcomes and the healthcare system.

44 Khoury, M. J., & Galea, S. (2016). Will Precision Medicine Improve Population Health? *JAMA*, 316(13), 1357–1358. <https://doi.org/10.1001/jama.2016.12260>

45 Weeramanthri, T. S., Dawkins, H. J. S., Baynam, G., Bellgard, M., Gudes, O., & Semmens, J. B. (2018). Editorial: Precision Public Health. *Frontiers in Public Health*, 6. <https://www.frontiersin.org/articles/10.3389/fpubh.2018.00121>

Figure 7: Summary of the potential value of PH/PM approaches across the patient journey



Source: CRA analysis

Recognising that there is a perception that PH/PM approaches are only helpful for a few people and are generally not cost-effective, this report presents a different perspective on the value that PH/PM bring to health systems and society in selected disease areas. The cost-effectiveness of PH/PM approaches is a highly debated topic, as the available evidence is mixed. Some studies suggest that PH/PM interventions are less cost-effective compared to usual care, while others argue that PH/PM leads to more health gains than non-personalized approaches. For example, a study by Vellekoop et al. (2022) found that personalised medicine leads to more health benefits than non-personalized approaches, but its costs, particularly for gene therapies, can result in zero to negative incremental net monetary benefit.⁴⁶ However, it is important to exercise caution when interpreting the results from this study as the narrow scope and study limitations may impact the certainty and generalisation of the results. The study only focuses on PH/PM approaches in genetic and genomic "test and treatment" combinations and does not consider the extended value in areas such as prevention and patient management that are enabled by the infrastructure and approaches of PH/PM. Additionally, methodological inconsistencies in the analysis of health benefits and net monetary benefit (NMB) estimation may also impact the accuracy of the results. Overall, the cost-effectiveness of PH/PM interventions varies widely across different types of interventions and therapy areas.^{47,48}

46 Vellekoop, H., Versteegh, M., Huygens, S., Ramos, I. C., Szilberhorn, L., Zelei, T., Nagy, B., Tsiachristas, A., Koleva-Kolarova, R., Wordsworth, S., & Mølken, M. R. (2022). The Net Benefit of Personalized Medicine: A Systematic Literature Review and Regression Analysis. *Value in Health*, 25(8), 1428–1438. <https://doi.org/10.1016/j.jval.2022.01.006>

47 Khoury, M. J., & Galea, S. (2016). Will Precision Medicine Improve Population Health? *JAMA*, 316(13), 1357–1358. <https://doi.org/10.1001/jama.2016.12260>

48 Kasztura, M., Richard, A., Bempong, N.-E., Loncar, D., & Flahault, A. (2019). Cost-effectiveness of precision medicine: A scoping review. *International Journal of Public Health*, 64(9), 1261–1271. <https://doi.org/10.1007/s00038-019-01298-x>





2.1.1. Cancers

There is a substantial amount of literature on the use of PH/PM approaches for the management of cancers across the patient care pathway. We found over 80 papers on the value of PH/PM approaches along patient care pathways for cancers, including breast, lung, colorectal and acute myeloid leukaemia. The papers provide evidence of the value of PH/PM approaches in practice. Examples of the use of PH/PM approaches across selected cancer types along the patient care pathway are in Annex 5.4.

Evidence of value of precision health (PH) and precision medicine (PM) approaches in selected cancer types

In selected cancer types, we found evidence to suggest that value accrues from PH/PM approaches in all the nine pre-identified value dimensions, although this value varies across the patient care pathway. Table 2 provides an overview of available evidence.

Table 2: Summary of value of PH/PM across patient care pathway for selected cancers

	 Prevention/ Screening	 Diagnosis	 Treatment	 Patient management & care
Better understanding of disease pathology	✓	✓	✓	✓
Improved disease prevention	✓	✓		✓
Better patient stratification and risk profiling	✓	✓	✓	✓
Improved clinical effectiveness	✓	✓	✓	✓
Reduced adverse events		✓	✓	✓
Efficiency in resource allocation, cost savings		✓	✓	✓
Improved patient management		✓	✓	✓
Increased socio-economic value (productivity)	✓	✓	✓	✓
Driving innovation ecosystem	✓	✓	✓	✓

Source: CRA analysis

✓ – evidence of value

Better understanding of disease pathology: Cancer is a disease of the human genome caused by an interplay of multiple genetic and epigenetic factors, including DNA mutations inherited or acquired that occur throughout life. PH/PM plays a critical role in improving

understanding of a tumour mutational profile which is important for diagnosis, prognosis and informing therapeutic and management options.^{49,50}

Improved disease prevention: Genetic testing for BRCA 1 and 2 as well as PALB2 genes, helps in risk stratification, thereby enabling targeted screening and improving disease prevention.⁵¹ PALB2 gene mutation predicts the risk of breast cancer ranging from 40% to 60% in a person's lifetime, which is much better than traditional approaches.⁵²

Better patient stratification and risk profiling: The development of precision risk-profiling models like the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), BRCAPRO⁵³ and the International Breast Cancer Intervention Study (IBIS) was found to be better than traditional methods thereby improving cancer risk reduction and prevention efforts.⁵⁴ The revision of risk stratification models based on PH/PM approach to include breast density as a significant risk factor for cancer development has improved cancer prevention.⁵⁵

Improved clinical effectiveness: Targeted and enhanced screening programmes for breast cancer, lung cancer and colorectal cancer have been found to improve survival rate with a mortality reduction of at least 30% and a 40% lower risk of advanced disease in breast cancer.^{56,57} Symptom monitoring during chemotherapy via web-based patient-reported outcomes (PROs) has demonstrated to lengthen survival in lung cancer.⁵⁸

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- 49 Krzyszczyk, P., Acevedo, A., Davidoff, E. J., Timmins, L. M., Marrero-Berrios, I., Patel, M., White, C., Lowe, C., Sherba, J. J., Hartmanshenn, C., O'Neill, K. M., Balter, M. L., Fritz, Z. R., Androulakis, I. P., Schloss, R. S., & Yarmush, M. L. (2018). The growing role of precision and personalized medicine for cancer treatment. *Technology*, 6(3-4), 79–100. <https://doi.org/10.1142/S2339547818300020>
- 50 Enabling Precision Medicine in Oncology. (n.d.). Retrieved October 19, 2022, from <https://emea.illumina.com/destination/Precision-Oncology.html>
- 51 Population-scale DNA test paves way to personalised medicine | Research and Innovation. (n.d.). Retrieved October 10, 2022, from <https://ec.europa.eu/research-and-innovation/en/projects/success-stories/all/population-scale-dna-test-paves-way-personalised-medicine>
- 52 Harris, E. E. R. (2018). Precision Medicine for Breast Cancer: The Paths to Truly Individualized Diagnosis and Treatment. *International Journal of Breast Cancer*, 2018, 4809183. <https://doi.org/10.1155/2018/4809183>
- 53 It is a statistical model, with associated software, for assessing the probability that an individual carries a germline deleterious mutation of the BRCA1 and BRCA2 genes, based on family history of breast and ovarian cancer
- 54 Bertier, G., Carrot-Zhang, J., Ragoussis, V., & Joly, Y. (2016). Integrating precision cancer medicine into healthcare—Policy, practice, and research challenges. *Genome Medicine*, 8(1), 108. <https://doi.org/10.1186/s13073-016-0362-4>
- 55 Farina, E., Nabhen, J. J., Dacoregio, M. I., Batalini, F., & Moraes, F. Y. (n.d.). An overview of artificial intelligence in oncology. *Future Science OA*, 8(4), FSO787. <https://doi.org/10.2144/foa-2021-0074>
- 56 Trimboli, R. M., Giorgi Rossi, P., Battisti, N. M. L., Cozzi, A., Magni, V., Zanardo, M., & Sardanelli, F. (2020). Do we still need breast cancer screening in the era of targeted therapies and precision medicine? *Insights into Imaging*, 11(1), 105. <https://doi.org/10.1186/s13244-020-00905-3>
- 57 Beeston, A. (2022, June 27). Enhanced breast screening improved survival. NIHR Evidence. https://doi.org/10.3310/nihrevidence_51612
- 58 Denis, F., Basch, E., Septans, A.-L., Bennouna, J., Urban, T., Dueck, A. C., & Letellier, C. (2019). Two-Year Survival Comparing Web-Based Symptom Monitoring vs Routine Surveillance Following Treatment for Lung Cancer. *JAMA*, 321(3), 306–307. <https://doi.org/10.1001/jama.2018.18085>

Biomarker-based testing is known to improve treatment selection strategy and treatment response (slower cancer growth and prolonged survival) for many cancer types.^{59,60,61,62,63} For example, application of multi-gene assays in breast cancer management provides a more accurate prediction of the risk of local-regional recurrence to inform patient selection for adjuvant radiotherapy or surgery, thereby improving clinical effectiveness and OS.⁶⁴ Patients with lung cancer who received a companion diagnostic (a device which is essential for the safe and effective use of a corresponding medicinal product) to guide initial treatment had a threefold greater survival advantage than patients who were not tested based on a 7-year data from the largest real world evidence study in NSCLC.⁶⁵ Epi proColon 2.0 CE was found to have a range of sensitivity (75-81%) and specificity (96-99%) much higher than comparator methods.⁶⁶ Testing all women with breast cancer for BReast CAncer gene (BRCA) mutations would save 3,069 lives annually (663 in UK; 2,406 in US) from breast and ovarian cancers at a Quality Adjusted Life Year (QALY) well below the standard thresholds.⁶⁷

Other patient-reported outcome measures such as recovery, functional improvement, emotional well-being as well as overall QoL have also been found to improve with use of precision oncology approaches across a number of cancer types. For example, in patients receiving larotrectinib (a targeted therapy) for Neurotrophic Tyrosine Receptor Kinase (NTRK) fusion-positive cancers, QoL was seen to improve within 60 days of treatment.⁶⁸

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- 59 Schwaederle, M., Zhao, M., Lee, J. J., Lazar, V., Leyland-Jones, B., Schilsky, R. L., Mendelsohn, J., & Kurzrock, R. (2016). Association of Biomarker-Based Treatment Strategies With Response Rates and Progression-Free Survival in Refractory Malignant Neoplasms: A Meta-analysis. *JAMA Oncology*, 2(11), 1452–1459. <https://doi.org/10.1001/jamaoncol.2016.2129>
- 60 Lehmann, C. (2018). Quantifying the Benefits of Precision Oncology. *Targeted Therapies in Oncology*, 7(11). <https://www.targetedonc.com/view/quantifying-the-benefits-of-precision-oncology>
- 61 Testa, U., Pelosi, E., & Castelli, G. (2021). Precision Medicine Treatment in Acute Myeloid Leukemia Is Not a Dream. *Hemato*, 2(1), Article 1. <https://doi.org/10.3390/hemato2010008>
- 62 Supporting Precision Oncology. (n.d.). Retrieved October 11, 2022, from <https://www.iqvia.com/insights/the-iqvia-institute/reports/supporting-precision-oncology>
- 63 Gavan, S. P., Thompson, A. J., & Payne, K. (2018). The economic case for precision medicine. *Expert Review of Precision Medicine and Drug Development*, 3(1), 1–9. <https://doi.org/10.1080/23808993.2018.1421858>
- 64 Harris, E. E. R. (2018). Precision Medicine for Breast Cancer: The Paths to Truly Individualized Diagnosis and Treatment. *International Journal of Breast Cancer*, 2018, 4809183. <https://doi.org/10.1155/2018/4809183>
- 65 John, A., Shah, R. A., Wong, W. B., Schneider, C. E., & Alexander, M. (2020). Value of Precision Medicine in Advanced Non-Small Cell Lung Cancer: Real-World Outcomes Associated with the Use of Companion Diagnostics. *The oncologist*, 25(11), e1743–e1752. <https://doi.org/10.1634/theoncologist.2019-0864>
- 66 Lamb, Y. N., & Dhillon, S. (2017). Epi proColon® 2.0 CE: A Blood-Based Screening Test for Colorectal Cancer. *Molecular Diagnosis & Therapy*, 21(2), 225–232. <https://doi.org/10.1007/s40291-017-0259-y>
- 67 Manchanda R, Patel S, Antoniou AC, et al. Cost-effectiveness of population based BRCA testing with varying Ashkenazi Jewish ancestry. *Am J Obstet Gynecol*. 2017;217(5):578.e1-578.e12. doi:10.1016/j.ajog.2017.06.038
- 68 Lassen, U. N., Makaroff, L. E., Stenzinger, A., Italiano, A., Vassal, G., Garcia-Foncillas, J., & Avouac, B. (2021). Precision oncology: a clinical and patient perspective. *Future oncology (London, England)*, 17(30), 3995–4009. <https://doi.org/10.2217/fo-2021-0688>

Targeted (matched) therapies improve progression-free survival (PFS) and OS compared to those without matched therapies across many cancer types.^{69,70,71,72,73,74,75,76,77,78} For example, imatinib (a targeted therapy) has been found to have remarkable effectiveness for patients with chronic myeloid leukaemia (CML) with improved overall survival rates of 90% over 5 years and 88% over 8 years.^{79,80}

Reduced adverse events: Treatment of advanced solid organ malignancies with targeted immunotherapy is associated with a lower risk of adverse events compared to traditional chemotherapy.⁸¹ In addition, clinical decision support systems (a form of precision clinical management support system) have been found to reduce the incidence of adverse events^{82,83}

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- 69 Precision oncology isn't on its way. It's already here. (n.d.). Retrieved October 11, 2022, from <https://www.nature.com/articles/d42473-021-00010-z>
- 70 Shin, S. H., Bode, A. M., & Dong, Z. (2017). Precision medicine: The foundation of future cancer therapeutics. *Npj Precision Oncology*, 1(1), Article 1. <https://doi.org/10.1038/s41698-017-0016-z>
- 71 Bui KT et al. Targeted molecular treatments in non-small cell lung cancer: A clinical guide for oncologists. *J Clin Med*. 2018;7(8):192.
- 72 Peters S et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2017;377(9):829-38.
- 73 Nassar, S. F., Raddassi, K., Ubhi, B., Doktorski, J., & Abulaban, A. (2020). Precision Medicine: Steps along the Road to Combat Human Cancer. *Cells*, 9(9), 2056. <https://doi.org/10.3390/cells9092056>
- 74 Lassen, U. N., Makaroff, L. E., Stenzinger, A., Italiano, A., Vassal, G., Garcia-Foncillas, J., & Avouac, B. (2021). Precision oncology: A clinical and patient perspective. *Future Oncology*, 17(30), 3995–4009. <https://doi.org/10.2217/fon-2021-0688>
- 75 Cost-effectiveness of precision medicine in gastrointestinal stromal tumor and gastric adenocarcinoma—Zeichner—*Journal of Gastrointestinal Oncology*. (n.d.). Retrieved October 11, 2022, from <https://jgo.amegroups.com/article/view/7609/11528>
- 76 Zhou, Z., & Li, M. (2022). Targeted therapies for cancer. *BMC Medicine*, 20(1), 90. <https://doi.org/10.1186/s12916-022-02287-3>
- 77 Wilsdon, T., Barron, A., Edwards, G. & Lawlor Charles River Associates, R. The benefits of personalised medicine to patients, society and healthcare systems Final Report. (2018)
- 78 Johnson DH et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 2004;22(11):2184-91.
- 79 Sparano JA, Gray RJ, Makower DF et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. *N Engl J Med* 379(2), 111–121 (2018)
- 80 Ezeife, D., Spackman, E., Juergens, R., Laskin, J., Agulnik, J., Hao, D., Laurie, S., Law, J., Le, L., Kiedrowski, L., Melosky, B., Shepherd, F. A., Cohen, V., Wheatley-Price, P., Vandermeer, R., Li, J., Fernandes, R., Shokoohi, A., Lanman, R., & Leigh, N. (2021). OA16.02 The Economic Value of Liquid Biopsy for Genomic Profiling in Advanced Non-Small Cell Lung Cancer. *Journal of Thoracic Oncology*, 16(10), S876. <https://doi.org/10.1016/j.jtho.2021.08.087>
- 81 Magee, D. E., Hird, A. E., Klaassen, Z., Sridhar, S. S., Nam, R. K., Wallis, C. J. D., & Kulkarni, G. S. (2020). Adverse event profile for immunotherapy agents compared with chemotherapy in solid organ tumors: a systematic review and meta-analysis of randomized clinical trials. *Annals of oncology : official journal of the European Society for Medical Oncology*, 31(1), 50–60. <https://doi.org/10.1016/j.annonc.2019.10.008>
- 82 Wilsdon, T., Barron, A., Edwards, G. & Lawlor Charles River Associates, R. The benefits of personalised medicine to patients, society and healthcare systems Final Report. (2018)
- 83 Shankaran V. Conference presentation at the Gastrointestinal Cancers Symposium. January 2009. Medscape website. <http://www.medscape.com/viewarticle/586946>

Efficiency in resource allocation, cost savings and cost-effectiveness: Available evidence suggests that precision oncology lowers average healthcare costs (reduction of approximately 20% comparing the target treatment group and control group – standard chemotherapy or best supportive care), resource utilisation and end-of-life costs for refractory cancer patients.⁸⁴ The use of genetic tests for KRAS gene in patients with metastatic colorectal cancer is found to yield significant healthcare savings.⁸⁵ There are cost savings that could accrue from targeted therapy in terms of reducing the use of ineffective therapies for patients and reducing hospital stays.⁸⁶ For example, treatment with adjuvant imatinib (a targeted therapy) for one year after surgical resection of KIT-mutated gastrointestinal cancers reduced costs associated with cancer recurrence by 11.7 – 21.9%.⁸⁷ The Institut National du Cancer (INCa) in France spent €1.7 million testing for EGFR biomarkers in over 16,000 lung cancer patients. Analysis of test outcomes revealed that approximately 10% of patients tested would respond to available treatments (gefitinib or erlotinib). By not using gefitinib or erlotinib for the 90% who tested negative for EGFR, about €69 million was made in treatment cost savings.⁸⁸ An analysis of the use of a gene panel predictive test to determine the likely benefit from chemotherapy in 592 breast cancer patients within the Irish Health Service showed a 58% net reduction in chemotherapy and net savings of €793,565 in just one year.⁸⁹

A study on the management of advanced NSCLC reveals that while PM approaches may lead to increased costs for biomarker testing and medicines in all countries, other healthcare costs are decreased, notably for the treatment of adverse events and end-of-life care.⁹⁰ Other studies also revealed that cost savings can be achieved from reduced adverse events. For example, an analysis from a large Irish private hospital revealed that the cost of hospital admission for severe chemotherapy-related toxicity was significantly higher than the cost of prospective testing for risk of toxicity. The analysis found that the financial implications of pre-screening patients for a genetic predisposition to severe side effects from fluoropyrimidine chemotherapy are noteworthy. With a cost of €23,718 for

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- 84 Haslem, D. S., Chakravarty, I., Fulde, G., Gilbert, H., Tudor, B. P., Lin, K., Ford, J. M., & Nadauld, L. D. (2018). Precision oncology in advanced cancer patients improves overall survival with lower weekly healthcare costs. *Oncotarget*, 9(15), 12316–12322. <https://doi.org/10.18632/oncotarget.24384>
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- 86 Wilsdon, T., Barron, A., Edwards, G. & Lawlor Charles River Associates, R. The benefits of personalised medicine to patients, society and healthcare systems Final Report. (2018)
- 87 Lassen, U. N., Makaroff, L. E., Stenzinger, A., Italiano, A., Vassal, G., Garcia-Foncillas, J., & Avouac, B. (2021). Precision oncology: A clinical and patient perspective. *Future Oncology*, 17(30), 3995–4009. <https://doi.org/10.2217/fon-2021-0688>
- 88 Nowak, F. (2012). Personalised medicine: A nationwide initiative for an equal access to cancer treatment in France. Presentation at EuroBioForum 2012
- 89 Smyth, L., Watson, G., Walsh, E. M., Kelly, C. M., Keane, M., Kennedy, M. J., Grogan, L., Hennessy, B. T., O'Reilly, S., Coate, L. E., O'Connor, M., Quinn, C., Verleger, K., Schoeman, O., O'Reilly, S., & Walshe, J. M. (2015). Economic impact of 21-gene recurrence score testing on early-stage breast cancer in Ireland. *Breast cancer research and treatment*, 153(3), 573–582. <https://doi.org/10.1007/s10549-015-3555-4>
- 90 Hofmarcher, T., Malmberg, C., & Lindgren, P. (2023). A global analysis of the value of precision medicine in oncology – The case of non-small cell lung cancer. *Frontiers in Medicine*, 10. <https://doi.org/10.3389/fmed.2023.1119506>

universal screening versus €232,061 in hospitalization expenses for side effect management, it demonstrates a significant opportunity for cost savings.⁹¹ This approach has been recognized and endorsed by NHS England since 2020, further emphasizing the tangible cost benefits of precision medicine in healthcare.⁹²

Similarly, AI-facilitated precision treatment fosters efficient use of healthcare resources by predicting treatment responses.⁹³ The reduction in the incidence of adverse events with the use of precision approaches in patient management is associated with cost savings from unnecessary usage of healthcare resources.⁹⁴ The use of clinical decision support systems has been found to reduce average cost of managing lung cancer patient by \$17,000.⁹⁵ Although available evidence suggests that the cost of targeted therapies remains significant, the use of clinical utility frameworks for precision oncology can aid the appropriate selection of the tumour entity, the clinical setting, and the alteration to be targeted, thus contributing to the overall cost-effectiveness of precision approaches in patient management.⁹⁶

The cost-effectiveness of precision oncology approaches varies across technology and cancer type. Precision prevention through the use of unselected multigene testing for all women with breast cancer to identify more cancer susceptibility gene (CSG) carriers has been found to be extremely cost-effective.⁹⁷ Many studies have found that next-generation sequencing (NGS) is cost-effective at a willingness-to-pay threshold of \$50,000 or \$100,000 per QALY gain.⁹⁸ The use of unselected BRCA1/BRCA2/PALB2 testing at breast cancer diagnosis was extremely cost-effective compared with BRCA1/BRCA2 testing based on clinical criteria or family history for UK and US health systems, with incremental cost-effectiveness ratios of £10 464 or £7216 and \$65 661 or \$61 618 per quality-adjusted life-year. One year's unselected panel genetic testing could prevent 2101 cases of breast

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- 91 Murphy, C., Byrne, S., Ahmed, G., Kenny, A., Gallagher, J., Harvey, H., O'Farrell, E., & Bird, B. (2018). Cost Implications of Reactive Versus Prospective Testing for Dihydropyrimidine Dehydrogenase Deficiency in Patients With Colorectal Cancer: A Single-Institution Experience. *Dose-response : a publication of International Hormesis Society*, 16(4), 1559325818803042. <https://doi.org/10.1177/1559325818803042>
- 92 England NHS. Clinical commissioning urgent policy statement Pharmacogenomic testing for DPYD polymorphisms with fluoropyrimidine therapies. London: NHS England; 2020
- 93 Farina, E., Nabhen, J. J., Dacoregio, M. I., Batalini, F., & Moraes, F. Y. (n.d.). An overview of artificial intelligence in oncology. *Future Science OA*, 8(4), FSO787. <https://doi.org/10.2144/foa-2021-0074>
- 94 Bowman, K. W. D., Landry Signé, and Diana M. (2022, January 4). Advancing precision medicine through agile governance. Brookings. <https://www.brookings.edu/research/advancing-precision-medicine-through-agile-governance/>
- 95 Nascimento, I. J. B. do, Marcolino, M. S., Abdulazeem, H. M., Weerasekara, I., Azzopardi-Muscat, N., Gonçalves, M. A., & Novillo-Ortiz, D. (2021). Impact of Big Data Analytics on People's Health: Overview of Systematic Reviews and Recommendations for Future Studies. *Journal of Medical Internet Research*, 23(4), e27275. <https://doi.org/10.2196/27275>
- 96 Christofyllakis, K., Bittenbring, J. T., Thurner, L., Ahlgrimm, M., Stilgenbauer, S., Bewarder, M., & Kaddu-Mulindwa, D. (2022). Cost-effectiveness of precision cancer medicine-current challenges in the use of next generation sequencing for comprehensive tumour genomic profiling and the role of clinical utility frameworks (Review). *Molecular and Clinical Oncology*, 16(1), 21. <https://doi.org/10.3892/mco.2021.2453>
- 97 Sun, L., Cui, B., Wei, X., Sadique, Z., Yang, L., Manchanda, R., & Legood, R. (2022). Cost-Effectiveness of Genetic Testing for All Women Diagnosed with Breast Cancer in China. *CANCERS*, 14(7), Article 7.
- 98 Weymann, D., Pataky, R., & Regier, D. A. (2018). Economic Evaluations of Next-Generation Precision Oncology: A Critical Review. *JCO Precision Oncology*, 2, 1–23. <https://doi.org/10.1200/PO.17.00311>

or ovarian cancer and 633 deaths in the United Kingdom and 9733 cases and 2406 deaths in the United States.⁹⁹ AI-powered colonoscopy is found to be a cost-effective intervention by efficiently detecting benign polyps that do not require surgical intervention.¹⁰⁰

Improved patient management: Clinical decision support systems have been found to improve overall patient management as well as decrease hospital stay in cancer management.¹⁰¹ For example, PH/PM approaches could decrease the length of hospital stays with an average stay of 3-4 days for patients receiving PH/PM-facilitated care compared with 7 days for patients not receiving PM-facilitated care.¹⁰² The use of measurable residual disease (MRD), as a prognostic, predictive, monitoring, and efficacy-response assessment has increasingly become an important biomarker in the management of patients with leukaemias.^{103,104} Circulating tumour DNA helps to predict treatment response and/or disease relapse in patients with haematological malignancies.¹⁰⁵

Improvement in the clinical management of NSCLC has been found with the use of PH/PM approaches, like the application of targeted therapy based on molecular profiling.¹⁰⁶

The use of AI and machine learning tools in digital pathology, such as digitizing whole-slide images of tissue, enables the mining of subvisual morphometric phenotypes to improve patient management.¹⁰⁷

Increased socio-economic value (productivity): Dzau et al. (2015), using the Health Economics Medical Innovation Simulation, found that PH/PM innovation could generate

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- 99 Sun L, Brentnall A, Patel S, et al. A Cost-effectiveness Analysis of Multigene Testing for All Patients With Breast Cancer. *JAMA Oncol.* 2019;5(12):1718–1730. doi:10.1001/jamaoncol.2019.3323
- 100 Farina, E., Nabhen, J. J., Dacoregio, M. I., Batalini, F., & Moraes, F. Y. (n.d.). An overview of artificial intelligence in oncology. *Future Science OA*, 8(4), FSO787. <https://doi.org/10.2144/foa-2021-0074>
- 101 Elliott, R. A., Camacho, E., Jankovic, D., Sculpher, M. J., & Faria, R. (2021). Economic analysis of the prevalence and clinical and economic burden of medication error in England. *BMJ Quality & Safety*, 30(2), 96–105. <https://doi.org/10.1136/bmjqs-2019-010206>
- 102 Elliott, R. A., Camacho, E., Jankovic, D., Sculpher, M. J., & Faria, R. (2021). Economic analysis of the prevalence and clinical and economic burden of medication error in England. *BMJ Quality & Safety*, 30(2), 96–105. <https://doi.org/10.1136/bmjqs-2019-010206>
- 103 Walter RB, Ofra Y, Wierzbowska A, et al. Measurable residual disease as a biomarker in acute myeloid leukemia: theoretical and practical considerations. *Leukemia.* 2021;35(6):1529-1538
- 104 Maiti A, DiNardo CD, Wang SA, et al. Prognostic value of measurable residual disease after venetoclax and decitabine in acute myeloid leukemia. *Blood Adv.* 2021;5(7):1876-1883
- 105 Nakamura S, Yokoyama K, Yusa N, Ogawa M, Takei T, Kobayashi A, et al. Circulating tumor DNA dynamically predicts response and/or relapse in patients with hematological malignancies. *Int J Hematol.* (2018) 108:402–10. doi: 10.1007/s12185-018-2487-2
- 106 Brown, N. A., Aisner, D. L., & Oxnard, G. R. (2018). Precision Medicine in Non–Small Cell Lung Cancer: Current Standards in Pathology and Biomarker Interpretation. *American Society of Clinical Oncology Educational Book*, 38, 708–715. https://doi.org/10.1200/EDBK_209089
- 107 Bera, K., Schalper, K. A., Rimm, D. L., Velcheti, V., & Madabhushi, A. (2019). Artificial intelligence in digital pathology - new tools for diagnosis and precision oncology. *Nature reviews. Clinical oncology*, 16(11), 703–715. <https://doi.org/10.1038/s41571-019-0252-y>

hundreds of billions of Euros in value in the form of longer, healthier lives enjoyed by patients.¹⁰⁸

Driving innovation ecosystem: PH/PM concept creates an ecosystem where interaction between data science digital tools and gene editing technologies facilitates the development of novel interventions to enhance the delivery of healthcare solutions. Greater adoption of PM/PH, especially with appropriate data infrastructure to permit integration into healthcare delivery and R&D, will accelerate innovations in PM/PH, which will enhance its benefits. In addition, the PH/PM-driven ecosystem values data collection and analysis at scale, which facilitates a better understanding of disease aetiology and pathogenesis; identification of operational efficiencies in health systems; identification of unmet needs; and development and evaluation of new healthcare solutions.

Development of large genetic databases using specialised bioinformatics tools to predict functional effect of specific gene alterations such as the 1,000 genomes project, dbSNP, the Exome Aggregation Consortium (ExAC), and the Exome Variant Server are examples of how PH/PM is driving innovation.¹⁰⁹

The innovative use of AI technology to refine risk-stratification definitions significantly improves the accuracy of screening approaches. For instance, an artificial neural network model for colorectal cancer risk stratification showed improved accuracy when compared with current screening guidelines, by reducing false positives from 53% to 6% and false negatives from 35% to 5%.¹¹⁰

Virtual decision support tools such as Watson for Genomics have shown proof-of-concept for the speed and utility of cognitive computing in identifying actionable mutations.¹¹¹ In addition, genome sequencing technologies supported by AI capabilities are rapidly increasing the number of targetable molecular alterations in many cancer types.¹¹²

Development of new technologies such as the CRISPR/Cas system and cryo-electron microscopy (cryo-EM) has sharpened PH/PM capabilities to discover novel therapeutic targets for precision oncology.¹¹³ The number of clinical trials integrating pharmacogenomic and/or pharmacogenetic analysis for patient stratification to enhance predictive response, dosing and safety, has more than doubled in the last decade,

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- 108 Dzau, V. J., Ginsburg, G.S., Van Nuys, K., Agus, D., and Goldman, D. (2015). Aligning incentives to fulfill the promise of personalised medicine. *Lancet* 385(9982):2118-2119. [https://doi.org/10.1016/S0140-6736\(15\)60722-X](https://doi.org/10.1016/S0140-6736(15)60722-X)
- 109 Bertier, G., Carrot-Zhang, J., Ragoussis, V., & Joly, Y. (2016). Integrating precision cancer medicine into healthcare—Policy, practice, and research challenges. *Genome Medicine*, 8(1), 108. <https://doi.org/10.1186/s13073-016-0362-4>
- 110 Farina, E., Nabhen, J. J., Dacoregio, M. I., Batalini, F., & Moraes, F. Y. (n.d.). An overview of artificial intelligence in oncology. *Future Science OA*, 8(4), FSO787. <https://doi.org/10.2144/foa-2021-0074>
- 111 Passiglia, F., & Scagliotti, G. V. (2021). The evolving paradigm of precision medicine in lung cancer. *Current Opinion in Pulmonary Medicine*, 27(4), 249–254. <https://doi.org/10.1097/MCP.0000000000000778>
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- 113 Shin, S. H., Bode, A. M., & Dong, Z. (2017). Precision medicine: The foundation of future cancer therapeutics. *Npj Precision Oncology*, 1(1), Article 1. <https://doi.org/10.1038/s41698-017-0016-z>

representing more than 40% of oncology trials in 2019.^{114,115} AI could also potentially make clinical trials for PH/PM treatment more efficient, consequently reducing drug development costs and discovery of new treatment modalities.¹¹⁶

Machine learning technology facilitates development of computerised clinical decision support systems (DSS), and deep learning in oncology which has significantly improved process outcomes and improved patient management.¹¹⁷

Key role of precision health (PH) and precision medicine (PM) and metrics to assess its level of adoption in selected cancer types

Precision oncology has significantly revolutionised cancer management particularly with regard to diagnosis and therapeutics. The inherent variability of cancer development and progression has become increasingly clear, necessitating the evolution of the traditional approach to molecular characterisation of cancers to allow more targeted interventions with better outcomes and fewer unnecessary side effects.¹¹⁸ In the last two decades, there has been an acceleration in the development of targeted therapies with their companion diagnostics. This has markedly improved the prognosis, progression-free survival and overall survival of many cancer types.¹¹⁹ Based on findings from the review of the literature, we identified the application of precision cancer diagnostics and therapeutics as the most advanced and most applied element of PH/PM approaches in cancer care.¹²⁰

In Chapter 3, we assess the level of adoption of precision cancer therapeutics and diagnostics in selected countries and the enablers of faster adoption of these technologies. In terms of metrics for the assessment, we selected reimbursement of newly approved targeted therapeutics and their companion diagnostics (biomarkers). In consideration of disease areas with the most population health needs, the selection of targeted therapies and their companion diagnostics was based on oncogene-driven cancer mutations with the highest burden (prevalence and mortality). Breast cancer is the most diagnosed cancer

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- 114 Supporting Precision Oncology. (n.d.). Retrieved October 11, 2022, from <https://www.iqvia.com/insights/the-iqvia-institute/reports/supporting-precision-oncology>
- 115 Farina, E., Nabhen, J. J., Dacoregio, M. I., Batalini, F., & Moraes, F. Y. (n.d.). An overview of artificial intelligence in oncology. *Future Science OA*, 8(4), FSO787. <https://doi.org/10.2144/fsoa-2021-0074>
- 116 Farina, E., Nabhen, J. J., Dacoregio, M. I., Batalini, F., & Moraes, F. Y. (n.d.). An overview of artificial intelligence in oncology. *Future Science OA*, 8(4), FSO787. <https://doi.org/10.2144/fsoa-2021-0074>
- 117 Nascimento, I. J. B. do, Marcolino, M. S., Abdulazeem, H. M., Weerasekara, I., Azzopardi-Muscat, N., Gonçalves, M. A., & Novillo-Ortiz, D. (2021). Impact of Big Data Analytics on People's Health: Overview of Systematic Reviews and Recommendations for Future Studies. *Journal of Medical Internet Research*, 23(4), e27275. <https://doi.org/10.2196/27275>
- 118 Krzyszczak, P., Acevedo, A., Davidoff, E. J., Timmins, L. M., Marrero-Berrios, I., Patel, M., White, C., Lowe, C., Sherba, J. J., Hartmanshenn, C., O'Neill, K. M., Balter, M. L., Fritz, Z. R., Androulakis, I. P., Schloss, R. S., & Yarmush, M. L. (2018). The growing role of precision and personalized medicine for cancer treatment. *Technology*, 6(3-4), 79–100. <https://doi.org/10.1142/S2339547818300020>
- 119 Krzyszczak, P., Acevedo, A., Davidoff, E. J., Timmins, L. M., Marrero-Berrios, I., Patel, M., White, C., Lowe, C., Sherba, J. J., Hartmanshenn, C., O'Neill, K. M., Balter, M. L., Fritz, Z. R., Androulakis, I. P., Schloss, R. S., & Yarmush, M. L. (2018). The growing role of precision and personalized medicine for cancer treatment. *Technology*, 6(3-4), 79–100. <https://doi.org/10.1142/S2339547818300020>
- 120 Schwartzberg, L., Kim, E. S., Liu, D., & Schrag, D. (2017). Precision Oncology: Who, How, What, When, and When Not? *American Society of Clinical Oncology Educational Book*, 37, 160–169. https://doi.org/10.1200/EDBK_174176

accounting for 13.1% of all cancer diagnoses, while lung cancer accounts for the most cancer deaths (380,000 deaths).¹²¹ Among breast and lung cancers, HER2-positive cancers (breast) and EGFR-positive cancers (NSCLC) were selected as they are the most prevalent and most diagnosed oncogene-driven cancer types, respectively. Around 20% of breast cancer in women are HER2 positive¹²², and approximately 10% -15% of NSCLC patients in Europe have EGFR mutations.¹²³

2.1.2. Familial hypercholesterolaemia (FH)





FH is an inherited genetic disorder that causes high cholesterol levels from birth and, if left untreated, often leads to early cardiovascular disease.¹²⁴ PH/PM approaches allow for identifying and treating patients at high risk before the onset of disease. To demonstrate the value of PH/PM, we reviewed over 40 articles which illustrate the use and value of PH/PM approaches in FH. According to the literature, the most prominent value of PH/PM is in the screening of patients that are identified as being at high risk and in the prevention of disease. Examples of the use of PH/PM approaches in FH are in Annex 5.5.

Evidence of value of precision health (PH) and precision medicine (PM) approaches in FH

In FH, we found evidence to suggest value of PH/PM approaches in all the nine pre-identified value dimensions, but it is mostly concentrated in prevention and diagnosis. Table 3 provides a summary of available evidence across FH patient care pathway.

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- 121 Dyba, T., Randi, G., Bray, F., Martos, C., Giusti, F., Nicholson, N., Gavin, A., Flego, M., Neamtiu, L., Dimitrova, N., Negrão Carvalho, R., Ferlay, J., & Bettio, M. (2021). The European cancer burden in 2020: Incidence and mortality estimates for 40 countries and 25 major cancers. *European journal of cancer (Oxford, England: 1990)*, 157, 308–347. <https://doi.org/10.1016/j.ejca.2021.07.039>
- 122 Breast Cancer HER2 Status | What is HER2 Status? (n.d.). Retrieved October 11, 2022, from <https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-her2-status.html>
- 123 Van Sanden, S., Murton, M., Bobrowska, A. et al. Prevalence of Epidermal Growth Factor Receptor Exon 20 Insertion Mutations in Non-small-Cell Lung Cancer in Europe: A Pragmatic Literature Review and Meta-analysis. *Targ Oncol* 17, 153–166 (2022)
- 124 Pereira, A. C. (2019). A roadmap for familial hypercholesterolaemia control. *The Lancet Digital Health*, 1(8), e376-e377.

Table 3: Summary of value of PH/PM across patient care pathway for FH

	 Prevention/Screening	 Diagnosis	 Treatment	 Patient management & care
Better understanding of disease pathology			✓	✓
Improved disease prevention	✓	✓		
Better patient stratification and risk profiling	✓	✓		
Improved clinical effectiveness	✓	✓		
Reduced adverse events			✓	✓
Efficiency in resource allocation, cost savings	✓	✓		
Improved patient management			✓	✓
Increased socio-economic value (productivity)	✓			
Driving innovation ecosystem			✓	✓

Source: CRA analysis

✓ – evidence of value

Better understanding of disease biology: Precision diagnostic approaches, such as the use of high-throughput platforms for omics testing, have facilitated an increased understanding of molecular factors that characterise cardiovascular diseases. Cardiovascular phenotyping using omics testing helps in defining the phenotype of aberrant lipid profiles.¹²⁵

Improved disease prevention: The cascade testing approach, identifying an FH proband with subsequent testing of all at-risk relatives, a cycle that is repeated, or cascaded, through the family until all at-risk individuals are tested, can identify up to 80% of clinically suspected FH cases.¹²⁶ It is very useful in early detection of FH as well as prevention efforts for coronary artery disease.^{127,128} Application of genetic testing helps to identify

125 Leopold, J. A. (2022). Personalizing treatments for patients based on cardiovascular phenotyping. *Expert Review of Precision Medicine and Drug Development*, 0(0), 1–13. <https://doi.org/10.1080/23808993.2022.2028548>

126 Developing and Optimizing Innovative Tools to Address Familial Hypercholesterolemia Underdiagnosis | *Circulation: Genomic and Precision Medicine*. (n.d.). Retrieved October 11, 2022, from <https://www.ahajournals.org/doi/full/10.1161/CIRCGEN.120.003120>

127 Population-scale DNA test paves way to personalised medicine | *Research and Innovation*. (n.d.). Retrieved October 10, 2022, from <https://ec.europa.eu/research-and-innovation/en/projects/success-stories/all/population-scale-dna-test-paves-way-personalised-medicine>

128 Nordestgaard, B. G., & Benn, M. (2017). Genetic testing for familial hypercholesterolaemia is essential in individuals with high LDL cholesterol: Who does it in the world? *European Heart Journal*, 38(20), 1580–1583. <https://doi.org/10.1093/eurheartj/ehx136>

asymptomatic individuals with FH who may benefit from early intervention to prevent atherosclerotic CVD.^{129,130,131}

Better patient stratification and risk profiling: Genetic testing is valuable in stratification of patients with raised blood cholesterol into those due to environmental and/or polygenic factors and those due to a single genetic defect (monogenic).¹³² Risk stratification also helps to inform treatment modalities.

In addition to integrating information on lipid profiles and other patient information, such as family history, into electronic health records, machine learning tools can facilitate faster detection of FH.¹³³ Furthermore, a case-finding algorithm, FAMCAT in the UK, has been found to have better performance in FH screening and case finding compared with other approaches for FH case finding.¹³⁴

Precision screening through the use of machine learning and AI platforms (applied to electronic health records) has been found to better identify individuals with FH based on a combination of diagnostic codes, pharmacy records, clinical notes and laboratory results.¹³⁵ Evidence from Spain suggests that massive data screening and patient profiling are effective tools and are easily applicable in clinical practice for the early detection of patients with FH.¹³⁶

One of the benefits of risk stratification that includes the use of pharmacogenomics is to identify patients who will benefit the most from certain treatments. Statins have some adverse effects that are somewhat predictable based on phenotypic and genetic factors.

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- 129 Vrablik, M., Tichý, L., Freiberger, T., Blaha, V., Satny, M., & Hubacek, J. A. (2020). Genetics of Familial Hypercholesterolemia: New Insights. *Frontiers in Genetics*, 11. <https://www.frontiersin.org/articles/10.3389/fgene.2020.574474>
- 130 Knowles, J. W., Rader, D. J., & Khoury, M. J. (2017). Cascade Screening for Familial Hypercholesterolemia and the Use of Genetic Testing. *JAMA*, 318(4), 381–382. <https://doi.org/10.1001/jama.2017.8543>
- 131 Sturm, A. C., Knowles, J. W., Gidding, S. S., Ahmad, Z. S., Ahmed, C. D., Ballantyne, C. M., Baum, S. J., Bourbon, M., Carri, é A., Cuchel, M., de, F. S. D., Defesche, J. C., Freiberger, T., Hershberger, R. E., Hovingh, G. K., Karayan, L., Kastelein, J. J. P., Kindt, I., Lane, S. R., ... null, null. (2018). Clinical Genetic Testing for Familial Hypercholesterolemia. *Journal of the American College of Cardiology*, 72(6), 662–680. <https://doi.org/10.1016/j.jacc.2018.05.044>
- 132 Recommendations | Familial hypercholesterolaemia: Identification and management | Guidance | NICE. (n.d.). NICE. Retrieved October 11, 2022, from <https://www.nice.org.uk/guidance/cg71/chapter/Recommendations>
- 133 Pepplinkhuizen, S., Ibrahim, S., Vink, R., Groot, B., Stroes, E. S. G., Bax, W. A., & Cornel, J. H. (2020). Electronic health records to facilitate continuous detection of familial hypercholesterolemia. *Atherosclerosis*, 310, 83–87. <https://doi.org/10.1016/j.atherosclerosis.2020.07.022>
- 134 Akyea, R. K., Qureshi, N., Kai, J., Lusignan, S. de, Sherlock, J., McGee, C., & Weng, S. (2020). Evaluating a clinical tool (FAMCAT) for identifying familial hypercholesterolaemia in primary care: A retrospective cohort study. *BJGP Open*, 4(5). <https://doi.org/10.3399/bjgpopen20X101114>
- 135 Banda JM, Sarraju A, Abbasi F, Parizo J, Pariani M, Ison H, et al. Finding missed cases of familial hypercholesterolemia in health systems using machine learning. *NPJ Digit Med* [Internet]. 2019
- 136 Massive data screening is a second opportunity to improve the management of patients with familial hypercholesterolemia phenotype | *Clínica e Investigación en Arteriosclerosis (English Edition)*. (n.d.). Retrieved October 11, 2022, from <https://www.elsevier.es/en-revista-clinica-e-investigacion-arteriosclerosis-english-415-articulo-massive-data-screening-is-second-S2529912321000231>

Variation in genes involved in statins metabolic pathways may influence the therapeutic effectiveness of statins.¹³⁷

Improved clinical effectiveness: Early diagnosis through precision testing followed by cholesterol-lowering therapies (such as from childhood) can almost completely prevent the incidence of heart attacks during adulthood.¹³⁸ Evidence suggests that early commencement of cholesterol-lowering treatment can confer the same life expectancy as unaffected persons.¹³⁹ Research findings in the Netherlands demonstrate a remarkable decline in heart attack rates, up to 76%, among individuals with familial hypercholesterolemia (FH) and at risk of coronary artery disease when employing a precision approach involving early diagnosis and treatment with statins as a preventive measure.¹⁴⁰ In a cohort of children with FH that started cholesterol-lowering treatment in childhood and continued until age 40, only 0.5% of the treated children had heart disease, contrasting to 28% of their affected parents.¹⁴¹

Reduced adverse events: New methods for analyzing pharmacogenetics have expanded the monitoring of potential gene variations and their associated traits, leading to a better understanding of how genetic differences can affect the effectiveness of lipid-lowering therapies and patient outcomes.¹⁴² Lipid-lowering therapies are crucial to preventing such diseases. However, sometimes these medications don't work as expected or cause side effects that can range from moderate to life-threatening, leading some people to stop using them. Genetics play a role in this, as differences in patient genes can influence how they react to these medications. Lipid-lowering therapy, when guided genetically, not only boosts overall safety but also promotes adherence to the medication, ensuring long-term therapeutic effectiveness.¹⁴³

Efficiency in resource allocation, cost savings and cost-effectiveness: FH screening programmes have been found to be cost-effective in addition to generating substantial cost savings for healthcare systems in the long term. An analysis from Spain indicates that a genetic screening programme, supplemented by treatment, for the close relatives of

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- 137 Ahangari, N., Doosti, M., Ghayour Mobarhan, M., Sahebkar, A., Ferns, G. A., & Pasdar, A. (n.d.). Personalised medicine in hypercholesterolaemia: The role of pharmacogenetics in statin therapy. *Annals of Medicine*, 52(8), 462–470. <https://doi.org/10.1080/07853890.2020.1800074>
- 138 EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). *Lancet*. 2021 Sep 7:S0140-6736(21)01122-3. doi: 10.1016/S0140-6736(21)01122-3. Epub ahead of print. PMID: 34506743
- 139 Neil A, Cooper J, Betteridge J, et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. *Eur Heart J*. 2008;29(21):2625–2633.
- 140 Versmissen, J., Oosterveer, D. M., Yazdanpanah, M., Defesche, J. C., Basart, D. C., Liem, A. H., ... & Sijbrands, E. J. (2008). Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. *Bmj*, 337.
- 141 Luirink IK, Wiegman A, Kusters DM, Hof MH, Groothoff JW, de Groot E, Kastelein JJP, Hutten BA. 20-Year follow-up of statins in children with familial hypercholesterolemia. *N Engl J Med* 2019;381:1547–1556.
- 142 Hindi, N. N., Alenbawi, J., & Nemer, G. (2021). Pharmacogenomics variability of lipid-lowering therapies in familial hypercholesterolemia. *Journal of Personalized Medicine*, 11(9), 877.
- 143 Shatnawi, A., Kamran, Z., & Al-Share, Q. (2022). Pharmacogenomics of lipid-lowering agents: the impact on efficacy and safety. *Personalized Medicine*, (0).

individuals with FH is preferable to the alternative of no screening in terms of incremental cost-effectiveness.¹⁴⁴

In Spain, the UK and several other healthcare systems, cascade screening has been shown to be highly cost-effective.^{145,146} In the UK, a study found a reduction of the incremental cost-effectiveness ratio (ICER) from £5806 to £2280 with more extensive implementation of cascade testing, indicating that the intervention (in this case, the cascade testing) becomes more cost-effective. This shows that the ICER was reduced by approximately 60.7% when the number of relatives tested per index case increased. In practical terms, if cascade testing is implemented more widely, each pound spent on this intervention is expected to yield more health benefits.¹⁴⁵ Available evidence from the UK suggests that searching primary care databases for people at high risk of FH, followed by cascade testing, is also cost-effective.¹⁴⁷

Improved patient management: Evidence from several countries suggests that identifying a pathogenic mutation to inform treatment modalities leads to better adherence to statins and lowering LDL-c levels.^{148,149,150,151,152} Precision medicine offers the potential to significantly enhance the management of familial hypercholesterolemia (FH). One instance of this is seen in a patient diagnosed with FH through genetic testing. The testing revealed that the patient has a severe form of the disease, characterized by high LDL cholesterol levels that increase their risk for cardiovascular disease. In traditional treatment, the patient would be prescribed a standard dose of a lipid-lowering drug like a statin. However, in a precision medicine approach, the patient's genetic information is

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- 144 Cost-Effectiveness Analysis of a Genetic Screening Program in the Close Relatives of Spanish Patients With Familial Hypercholesterolemia | Revista Española de Cardiología. (n.d.). Retrieved October 11, 2022, from <https://www.revvespcardiol.org/en-cost-effectiveness-analysis-genetic-screening-program-articulo-13131647>
- 145 Kerr, M., Pears, R., Miedzybrodzka, Z., Haralambos, K., Cather, M., Watson, M., & Humphries, S. E. (2017). Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on data from familial hypercholesterolaemia services in the UK. *European Heart Journal*, 38(23), 1832–1839. <https://doi.org/10.1093/eurheartj/ehx111>
- 146 Lázaro, P., Pérez de Isla, L., Watts, G. F., Alonso, R., Norman, R., Muñoz, O., Fuentes, F., Mata, N., López-Miranda, J., González-Juanatey, J. R., Díaz-Díaz, J. L., Blasco, A. J., & Mata, P. (2017). Cost-effectiveness of a cascade screening program for the early detection of familial hypercholesterolemia. *Journal of Clinical Lipidology*, 11(1), 260–271. <https://doi.org/10.1016/j.jacl.2017.01.002>
- 147 Crosland, P., Maconachie, R., Buckner, S., McGuire, H., Humphries, S. E., & Qureshi, N. (2018). Cost-utility analysis of searching electronic health records and cascade testing to identify and diagnose familial hypercholesterolaemia in England and Wales. *Atherosclerosis*, 275, 80–87. <https://doi.org/10.1016/j.atherosclerosis.2018.05.021>
- 148 Long-term compliance with lipid-lowering medication after genetic screening for familial hypercholesterolemia <https://pubmed.ncbi.nlm.nih.gov/12523918/>
- 149 Umans-Eckenhausen MA, Defesche JC, van Dam MJ, Kastelein JJ. Long-term compliance with lipid-lowering medication after genetic screening for familial hypercholesterolemia. *Arch Intern Med.* (2003) 163:65–8. doi: 10.1001/archinte.163.1.65
- 150 Leren TP, Manshaus T, Skovholt U, Skodje T, Nossen IE, Teie C, et al. Application of molecular genetics for diagnosing familial hypercholesterolemia in Norway: results from a family-based screening program. *Semin Vasc Med.* (2004) 4:75–85. doi: 10.1055/s-2004-822989
- 151 Leren TP. Cascade genetic screening for familial hypercholesterolemia. *Clin Genet.* (2004) 66:483–7. doi: 10.1111/j.1399-0004.2004.00320.x
- 152 Umans-Eckenhausen MA, Defesche JC, Sijbrands EJ, Scheerder RL, Kastelein JJ. Review of first 5 years of screening for familial hypercholesterolaemia in the Netherlands. *Lancet* (2001) 357:165–8. doi: 10.1016/S0140-6736(00)03587-X

utilised to create a customized treatment plan. This may include a higher dose of medication or a combination of drugs specifically tailored to their genetic variant, as well as recommendations for lifestyle changes and monitoring.

Increased socio-economic value (productivity): Cardiovascular diseases (CVDs) have a significant impact on the European Union's (EU) economy, with an estimated cost of over €210 billion per year, according to a report by the European Heart Network. Of this total cost, healthcare expenses contribute to 53% (€111 billion), productivity losses account for 26% (€54 billion), and informal care of people with CVDs represents 21% (€45 billion).¹⁵³ Evidence suggests that screening programs may help reduce the economic burden of CVDs by identifying and managing risk factors for these conditions early on. Such programs have the potential to reduce healthcare costs and lost productivity, leading to improved health outcomes and economic benefits. A study from Spain shows that the national program for FH (NPFH), which involves total cholesterol measurement at the primary care level and the use of genetic testing in index cases and relatives, can prevent 847 coronary events and 203 deaths in a cohort of 9000 FH patients over a 10-year follow-up.¹⁵⁴ While quantifying the exact socio-economic value of FH screening programs can be challenging, cost-effectiveness analyses suggest these programs deliver substantial benefits through the prevention of serious health events, efficient identification of affected individuals, and improved quality of life. According to FH EUROPE (patient advocacy group), FH screening reduces the human, financial and societal burden of cardiovascular disease.¹⁵⁵

Driving innovation ecosystem: In addition to its potential to catalyze research into novel therapies such as PCSK9i by highlighting disease pathways, risk stratification using gene testing can also enable the detection of rare variants.^{156,157} This has the potential to drive innovation in the management of familial hypercholesterolemia (FH) by helping to identify individuals at increased risk of developing the condition and providing personalised treatment plans.

Key role of precision health (PH) and precision medicine (PM) and metrics to assess its level of adoption in FH

FH is a great example of a precision genetic approach to prevention and screening, showing real promise for public health. The most prominent value of PH/PM approaches in FH is observed in diagnosis and prevention of subsequent disease. Therefore, in Chapter 3 we assess the difference between selected countries in terms of the existence of national

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- 153 European Cardiovascular Disease Statistics 2017, <https://ehnheart.org/cvd-statistics.html#:~:text=Overall%20CVD%20is%20estimated%20to,care%20of%20people%20with%20CVD>.
- 154 Lázaro, P., de Isla, L. P., Watts, G. F., Alonso, R., Norman, R., Muñiz, O., ... & Mata, P. (2017). Cost-effectiveness of a cascade screening program for the early detection of familial hypercholesterolemia. *Journal of clinical lipidology*, 11(1), 260-271.
- 155 FH Europe, FH Paediatric screening in Europe – Paving the Way for Prevention and Cardiovascular Health; available at <https://fheurope.org/latest-news/fh-paediatric-screening-in-europe/>
- 156 Massive data screening is a second opportunity to improve the management of patients with familial hypercholesterolemia phenotype | Clínica e Investigación en Arteriosclerosis (English Edition). (n.d.). Retrieved October 11, 2022, from <https://www.elsevier.es/en-revista-clinica-e-investigacion-arteriosclerosis-english-415-articulo-massive-data-screening-is-second-S2529912321000231>
- 157 Akyea, R. K., Qureshi, N., Kai, J., Lusignan, S. de, Sherlock, J., McGee, C., & Weng, S. (2020). Evaluating a clinical tool (FAMCAT) for identifying familial hypercholesterolaemia in primary care: A retrospective cohort study. *BJGP Open*, 4(5). <https://doi.org/10.3399/bjgpopen20X101114>

screening programmes and the availability of genetic testing for patients at high risk of FH. In addition, we present two country case studies with best practices to enhance the use of genetic testing in children.





2.1.3. Type 1 diabetes mellitus (type 1 DM)

We identified several papers providing examples related to the use of PH/PM approaches along the type 1 DM patient care pathway and further evidence of the value of these approaches in practice. Continuous glucose monitoring (CGM), with advancements in sensor technologies and the discovery of novel biomarkers, increased the use of PH/PM approaches in type 1 DM patients. In the literature, evidence of different value dimensions for type 1 DM was found with a focus on better patient stratification, reducing adverse events and improving patient management. Examples of the use of PH/PM approaches in type 1 DM management are in Annex 5.6.

Evidence of value of precision health and precision medicine approaches in type 1 DM

Table 4 provides a summary of available evidence across type 1 DM patient care pathway.

Table 4: Summary of value of PH/PM across patient care pathway for type 1 DM

	 Prevention/ Screening	 Diagnosis	 Treatment	 Patient management & care
Better understanding of disease pathology				
Improved disease prevention	✓			
Better patient stratification and risk profiling		✓	✓	✓
Improved clinical effectiveness			✓	✓
Reduced adverse events	✓	✓	✓	✓
Efficiency in resource allocation, cost savings	✓	✓	✓	
Improved patient management		✓	✓	✓
Increased socio-economic value (productivity)		✓	✓	✓
Driving innovation ecosystem		✓	✓	✓

Source: CRA analysis

✓ – evidence of value

Improved disease prevention: It has been shown that early intervention after identification of individuals with two or more autoantibodies and dysglycaemia delayed the

onset of stage 3 disease by a median of 32.5 months compared to placebo control group in the study.¹⁵⁸

Better patient stratification and risk profiling: Islet autoantibody testing and type 1 diabetes genetic risk scores were shown to improve diagnostic accuracy and assist in discriminating between type 1, type 2 and other forms of diabetes. The use of additional biomarkers, such as the level of serum or urine C-peptide levels, further assists in diagnosis, patient reclassification and insulin withdrawal. The individual progressive trajectory of C-peptide loss over the immediate years post-diagnosis clearly separated type 1 diabetes from type 2 diabetes and improved patient management.¹⁵⁹ Genetic testing and identification of individual glucose patterns using continuous glucose monitoring have also been found to improve patient stratification and therapy selection.¹⁶⁰

Improved clinical effectiveness: The early identification, monitoring, and regular follow-up of high-risk individuals can reduce diabetic ketoacidosis (DKA) rates from 25–62% to 4–6%. Reductions in DKA rates have a potential longer-term impact in reducing HbA1c levels and risk of complications in type 1 DM patients.^{161,162,163} In addition, the use of biomarkers was shown to assist in better prediction of the treatment responders and non-responders in the clinical trials of immunotherapies including abatacept, alefacept, teplizumab and rituximab.¹⁶⁴

PM approaches were shown to identify the most suitable treatment based on patient stratification or assist cessation of unnecessary medication. Especially in the monogenic forms of type 1 DM, precision diagnosis has a key role in stopping unnecessary medication. In the case of individuals with the GCK-MODY (MODY2) form of monogenic type 1 DM, it is established that patients do not require, or respond to, oral medication.¹⁶⁵

In addition, PM approaches could also tackle the complexities due to disease heterogeneity. For example, in clinical trials, an immunotherapeutic agent, alefacept, was shown to improve C-peptide response and beta cell function; however, further studies showed that abatacept accelerates the disease progression in patients of Black African

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- 158 Herold KC, Bundy BN, Long SA, et al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes [published correction appears in N Engl J Med. 2020 Feb 6;382(6):586]. N Engl J Med. 2019;381(7):603-613. doi:10.1056/NEJMoa1902226
- 159 Carr ALJ, Evans-Molina C, Oram RA. Precision medicine in type 1 diabetes [published online ahead of print, 2022 Aug 22]. Diabetologia. 2022;10.1007/s00125-022-05778-3. doi:10.1007/s00125-022-05778-3
- 160 Klonoff DC, Florez JC, German M, Fleming A. The Need for Precision Medicine to be Applied to Diabetes. J Diabetes Sci Technol. 2020;14(6):1122-1128. doi:10.1177/1932296819894295
- 161 Alonso GT, Coakley A, Pyle L, Manseau K, Thomas S, Rewers A. Diabetic ketoacidosis at diagnosis of type 1 diabetes in Colorado children, 2010-2017. Diabetes Care 2020;43:117–121
- 162 Duca LM, Wang B, Rewers M, Rewers A. Diabetic ketoacidosis at diagnosis of type 1 diabetes predicts poor long-term glycemic control. Diabetes Care 2017;40:1249–1255
- 163 Winkler C, Schober E, Ziegler AG, Holl RW. Markedly reduced rate of diabetic ketoacidosis at onset of type 1 diabetes in relatives screened for islet autoantibodies. Pediatr Diabetes 2012;13:308–313
- 164 Deligne C, You S, Mallone R. Personalized Immunotherapies for Type 1 Diabetes: Who, What, When, and How? J Pers Med. 2022 Mar 29;12(4):542. doi: 10.3390/jpm12040542. PMID: 35455658; PMCID: PMC9031881.
- 165 Stride A, Shields B, Gill-Carey O, et al. Cross-sectional and longitudinal studies suggest pharmacological treatment used in patients with glucokinase mutations does not alter glycaemia. Diabetologia 2014;57:54–56

descent. Similarly, another immunotherapy agent, rituximab, was shown to be only effective in a minority of stage 3 patients for a maximum duration of 1 year. Efficacy of rituximab to delay disease progression seemed limited to younger cases, whereas abatacept showed efficacy at older disease onset. Therefore, age, race, or disease-onset-based stratification assists identification of more effective treatment for type 1 DM patients.¹⁶⁶

Reduced adverse events (and clinical complications): Early identification and disease management intervention in at-risk populations improved patient outcomes. Early disease management strategies were applied in a cohort of genetically at-risk children (DAISY - Diabetes Autoimmunity Study in the Young). Overall, only 3% of the DAISY children were hospitalised at diagnosis of type 1 DM compared to 44% of matched children in the community. Lower HbA1C levels were maintained within the normal range, much lower than the average HbA1C levels of type 1 DM children in the community.¹⁶⁷

Similarly, in another cohort study from Germany (BABYDIAB and Munich family study), when children screened positive for islet autoantibodies and followed closely, the rate of diabetic ketoacidosis was significantly reduced, though no difference in clinical outcomes was found after five years.¹⁶⁸

Continuous glucose monitoring has been instrumental in reducing clinical complications and adverse events related to type 1 DM. Multiple randomized clinical trials showed that the use of continuous glucose monitoring improves overall glycemic control and leads to significant reductions in hypoglycemia in type 1 DM patients.^{169, 170}

The use of machine learning algorithms was shown to reduce treatment burden and adverse events in type 1 DM patients. Integrating data on glucose, insulin, and meals can effectively predict glucose in paediatric patients in terms of numerical and clinical accuracy to allow patients to avoid adverse events.¹⁷¹ Another example of a machine learning tool predicts the progression to diabetic kidney disease with high accuracy using levels of

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- 166 den Hollander NHM, Roep BO. From Disease and Patient Heterogeneity to Precision Medicine in Type 1 Diabetes. *Front Med (Lausanne)*. 2022 Jul 12;9:932086. doi: 10.3389/fmed.2022.932086. PMID: 35903316; PMCID: PMC9314738.
- 167 Barker JM, Goehrig SH, Barriga K, et al. Clinical characteristics of children diagnosed with type 1 diabetes through intensive screening and follow-up. *Diabetes Care*. 2004;27(6):1399-1404. doi:10.2337/diacare.27.6.1399
- 168 Winkler C, Schober E, Ziegler AG, Holl RW. Markedly reduced rate of diabetic ketoacidosis at onset of type 1 diabetes in relatives screened for islet autoantibodies. *Pediatr Diabetes*. 2012;13(4):308-313. doi:10.1111/j.1399-5448.2011.00829.x
- 169 Pratley RE, Kanapka LG, Rickels MR, et al. Effect of Continuous Glucose Monitoring on Hypoglycemia in Older Adults With Type 1 Diabetes: A Randomized Clinical Trial. *JAMA*. 2020;323(23):2397-2406. doi:10.1001/jama.2020.6928
- 170 Miller KM, Kanapka LG, Rickels MR, et al. Benefit of Continuous Glucose Monitoring in Reducing Hypoglycemia Is Sustained Through 12 Months of Use Among Older Adults with Type 1 Diabetes. *Diabetes Technol Ther*. 2022;24(6):424-434. doi:10.1089/dia.2021.0503
- 171 D'Antoni F, Petrosino L, Sgarro F, et al. Prediction of Glucose Concentration in Children with Type 1 Diabetes Using Neural Networks: An Edge Computing Application. *Bioengineering (Basel)*. 2022;9(5):183. Published 2022 Apr 21. doi:10.3390/bioengineering9050183

albuminuria, glomerular filtration rate and retinopathy status at baseline in type 1 DM patients.¹⁷²

Efficiency in resource allocation, cost savings and cost-effectiveness: It is estimated that screening and follow-up would be cost-effective even if it would reduce the rate of diabetic ketoacidosis (DKA) by 20%, which would also lower glycated haemoglobin (HbA1c¹⁷³) by 0.1% over a lifetime. Considering these thresholds, screening may be cost-effective in areas in which DKA is highly prevalent and an infrastructure facilitating screening and monitoring exists.¹⁷⁴

Improved patient management: The use of biomarkers in patient stratification, such as the classification of patients based on individual C-peptide profiles, can potentially improve the decision-making of the start/cessation of insulin therapy and patient management in type 1 DM.¹⁷⁵ Moreover, with the advancements in monitoring and use of machine learning models, it was shown that algorithms based on a patient's unique glucose profile have excellent performance at predicting hypoglycaemia and hyperglycaemia and supporting young adults with type 1 DM to take control of their own care.¹⁷⁶ For type 1 DM patients, precision monitoring including biological markers (e.g., continuous glucose monitoring), behaviours (e.g., physical activity), diet, sleep, and psychophysiological stress using digital tools could deliver better clinical outcomes, improved disease management and reduced burden on healthcare providers.¹⁷⁷

Increased socio-economic value (productivity): A precision approach to diagnosis with appropriate standardised laboratory support and use of novel biomarkers has the potential to prevent inaccurate classification of types of diabetes and its likely long-lasting, adverse effects on mental health and quality of life, which will likely to positively impact socioeconomic outcomes.¹⁷⁸ Even non-severe hypoglycemic events have been shown to

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- 172 Al-Sari N, Kutuzova S, Suvitaival T, et al. Precision diagnostic approach to predict 5-year risk for microvascular complications in type 1 diabetes. *EBioMedicine*. 2022;80:104032. doi:10.1016/j.ebiom.2022.104032
- 173 Glycated haemoglobin (HbA1C) is an indication of average blood sugar (glucose) level for the past two to three months
- 174 McQueen RB, Geno Rasmussen C, Waugh K, et al. Cost and cost-effectiveness of large-scale screening for type 1 diabetes in Colorado. *Diabetes Care* 2020;43:1496–1503
- 175 Carr ALJ, Evans-Molina C, Oram RA. Precision medicine in type 1 diabetes [published online ahead of print, 2022 Aug 22]. *Diabetologia*. 2022;10.1007/s00125-022-05778-3. doi:10.1007/s00125-022-05778-3
- 176 Duckworth C, Guy MJ, Kumaran A, et al. Explainable Machine Learning for Real-Time Hypoglycemia and Hyperglycemia Prediction and Personalized Control Recommendations [published online ahead of print, 2022 Jun 13]. *J Diabetes Sci Technol*. 2022;19322968221103561. doi:10.1177/19322968221103561
- 177 Population-level management of type 1 diabetes via continuous glucose monitoring and algorithm-enabled patient prioritization: Precision health meets population health
<https://onlinelibrary.wiley.com/doi/10.1111/pedi.13256>
- 178 Chung WK, Erion K, Florez JC, et al. Precision medicine in diabetes: a Consensus Report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2020;63(9):1671-1693. doi:10.1007/s00125-020-05181-w

have substantial economic consequences leading to 8-16 hours of lost work time per month.¹⁷⁹

Continuous glucose monitoring decreased the time spent in hyperglycaemia and hypoglycemia, reduced the risk of severe hypoglycemia and improved quality of life.¹⁸⁰ Continuous glucose monitoring is becoming the standard of care for type 1 DM patients with recent updates in clinical guidelines such as the UK's National Institute for Health and Care Excellence (NICE) guidelines.¹⁸¹

Driving innovation ecosystem: With the increased use of precision approaches in type 1 DM patients, another potentially revolutionising milestone would be using cell therapies to prevent or reverse type 1 DM pathophysiology. Cell therapies, combined with next-generation genome-editing techniques, would allow the generation of cells that are able to escape from autoimmune responses and restore β -cell function¹⁸². Additional innovative treatments and new PH/PM tools in type 1 DM will likely result in breakthroughs in patient management in the following years.

Key role of precision health (PH) and precision medicine (PM) and metrics to assess its level of adoption in type 1 DM

Based on the analysis of available literature using our framework, we identified the use of precision monitoring tools (such as Flash glucose monitoring and continuous glucose monitoring) as among the most valuable adoptions of precision technology in the management of type 1 DM. This approach provides real-time measures of glycaemic variability and has been shown to significantly improve HbA1c levels, reduce the risk of severe hypoglycaemia, and improve quality of life. The time factor in precision health is a significant factor that can enhance the customization of care and make it more homeostatic by minimizing the delay between intervention and management, as evidenced by the use of real-time monitoring of blood glucose levels.

The adoption of this technology as a standard of care for all patients with type 1 DM has been recommended for improved patient management. Therefore, in Chapter 3, we evaluated selected countries based on reimbursement of continuous monitoring devices and digital therapeutics (mobile apps) used for the clinical monitoring of type 1 DM patients.

2.1.4. COVID-19

The use of digital tools and advanced genomic technologies was highly influential in the COVID-19 response of European countries. We found extensive literature with over 20 papers discussing PM/PH approaches in COVID-19 care pathway. In the literature, evidence of different value dimensions for COVID-19 was found to focus on a better

179 Brod, Meryl et al. "The impact of non-severe hypoglycemic events on work productivity and diabetes management." *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* vol. 14,5 (2011): 665-71. doi:10.1016/j.jval.2011.02.001

180 Carr ALJ, Evans-Molina C, Oram RA. Precision medicine in type 1 diabetes [published online ahead of print, 2022 Aug 22]. *Diabetologia*. 2022;10.1007/s00125-022-05778-3. doi:10.1007/s00125-022-05778-3

181 NICE (2015) Diabetes (type 1 and type 2) in children and young people: diagnosis and management. Available at www.nice.org.uk/guidance/ng18/chapter/Recommendations#type-1-diabetes. Accessed 9 Sep 2022





182 Loretelli C, Assi E, Seelam AJ, Ben Nasr M, Fiorina P. Cell therapy for type 1 diabetes. *Expert Opin Biol Ther*. 2020;20(8):887-897. doi:10.1080/14712598.2020.1748596

understanding of disease pathology and improved disease prevention. Examples of the use of PH/PM approaches in the COVID-19 response are in Annex 5.7.

Evidence of value of precision health (PH) and precision medicine (PM) approaches in COVID-19

Table 5 provides a summary of available evidence across COVID-19 patient care pathway.

Table 5: Summary of value of PH/PM across patient care pathway for COVID-19

	 Prevention/ Screening	 Diagnosis	 Treatment	 Patient management & care
Better understanding of disease pathology	✓	✓	✓	✓
Improved disease prevention	✓	✓		
Better patient stratification and risk profiling		✓	✓	✓
Improved clinical effectiveness			✓	✓
Reduced adverse events	✓	✓	✓	✓
Efficiency in resource allocation, cost savings	✓		✓	
Improved patient management	✓	✓	✓	✓
Increased socio-economic value (productivity)		✓		
Driving innovation ecosystem	✓			

Source: CRA analysis

✓ – evidence of value

Better understanding of disease pathology: Using PH/PM approaches to better understand disease pathology and symptomatology played a key role in preventing the disease worldwide. PCR testing and genetic sequencing helped reveal the emergence of different viral variants. Early identification of alpha variant and its significant mutations associated with increased transmission allowed authorities to have informed decisions to tighten restrictions in several European countries. Several countries used big data or digital tools such as the nationwide SCIFI-PEARL database in Sweden¹⁸³, a web-based surveillance survey in Switzerland¹⁸⁴ and COVID Symptoms survey in the UK¹⁸⁵ to identify

183 Hou C. Y. (2022). Four areas of health innovation boosted by the pandemic. *Nature medicine*, 28(7), 1326–1328. <https://doi.org/10.1038/s41591-022-01844-w>

184 Leal-Neto, O., Egger, T., Schlegel, M., Flury, D., Sumer, J., Albrich, W., Babouee Flury, B., Kuster, S., Vernazza, P., Kahlert, C., & Kohler, P. (2021). Digital SARS-CoV-2 Detection Among Hospital Employees: Participatory Surveillance Study. *JMIR public health and surveillance*, 7(11), e33576. <https://doi.org/10.2196/33576>

185 Sudre, C. H., Keshet, A., Graham, M. S., Joshi, A. D., Shilo, S., Rossman, H., Murray, B., Molteni, E., Klaser, K., Canas, L. D., Antonelli, M., Nguyen, L. H., Drew, D. A., Modat, M., Pujol, J. C., Ganesh, S., Wolf, J., Meir, T., Chan, A. T., Steves, C. J., ... Astley, C. M. (2021). Anosmia, ageusia, and other COVID-19-like symptoms in association with a positive SARS-CoV-2 test, across six national digital surveillance platforms: an observational study. *The Lancet. Digital health*, 3(9), e577–e586. [https://doi.org/10.1016/S2589-7500\(21\)00115-1](https://doi.org/10.1016/S2589-7500(21)00115-1)

key symptoms and improve the disease understanding. In addition, use of phylogenomic analysis of the virus in the UK allowed a better understanding of the contribution of the travel-associated strain introductions.¹⁸⁶

Improved disease prevention: The availability of SARS-CoV-2's whole-genome sequence has enabled the rapid development of molecular diagnostic techniques, playing a pivotal role in managing COVID-19. The advancements in genomics have facilitated the design of diagnostic assays such as RT-PCR, TMA, LAMP, and CRISPR/Cas-based tests, which use specific regions of the virus genome for accurate detection.¹⁸⁷ Genomic sequencing helps identify new variants of viruses, such as SARS-CoV-2 and provides crucial information on how the virus is evolving. Understanding these changes is vital to assess the risk they pose and adapt response strategies accordingly.¹⁸⁷ In addition, genomic sequencing can track the spread of a virus, allowing public health officials to understand transmission patterns and predict potential outbreaks. This information can then be used to implement targeted containment measures.¹⁸⁸ While contact tracing has been a long-established element of infectious disease control, the deployment of digital apps during the COVID-19 pandemic illustrated how mobile technology can enhance the accuracy and effectiveness of such efforts.

In the case of COVID-19 pandemic, it was estimated that contact tracing would reduce transmission of the virus by at least 10% in case 50% of new cases were detected and 50% of their contacts were isolated. With more efficient use of contact tracing and a higher frequency of contact isolation, it is possible to reduce transmission by more than 45%.¹⁸⁹ With the use of the National Health Service (NHS) COVID-19 app in the UK, it was estimated that every 1% increase in app downloads led to a 0.8-2.3% reduction in COVID-19 infections.¹⁹⁰

Better patient stratification and risk profiling: Using personalised wearable devices to continuously track an individual's physiological and behavioural metrics or advanced

186 du Plessis L, McCrone JT, Zarebski AE, et al. Establishment and lineage dynamics of the SARS-CoV-2 epidemic in the UK. *Science*. 2021;371(6530):708-712. doi:10.1126/science.abf2946

187 Saravanan, K. A., Panigrahi, M., Kumar, H., Rajawat, D., Nayak, S. S., Bhushan, B., & Dutt, T. (2022). Role of genomics in combating COVID-19 pandemic. *Gene*, 823, 146387.

188 Korber B., Fischer W.M., Gnanakaran S., Yoon H., Theiler J., Abfalterer W., et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. *Cell*. 2020;182:812–827.e19. doi: 10.1016/j.cell.2020.06.043

189 Siemens Healthineers. Moving toward precision in managing pandemics: 5 critical domains for success in public health. Issue 11 [siemens-healthineers.com/expanding-precision-medicine](https://www.siemens-healthineers.com/expanding-precision-medicine)

190 Wymant C, Ferretti L, Tsallis D, et al. The epidemiological impact of the NHS COVID-19 app. *Nature*. 2021;594(7863):408-412. doi:10.1038/s41586-021-03606-z

sensors to monitor heart/respiratory rate variations allowed distinguishing COVID-19 from other viral diseases or improved identification of long COVID-19 patients.^{191,192,193}

Precision medicine can help identify biomarkers that are associated with disease severity or treatment response in COVID-19. For example, biomarkers such as cytokines, D-dimer, and ferritin have been used to guide treatment decisions and predict disease progression.¹⁹⁴

Reduced adverse events: The interplay between pharmacogenomics and the use of Remdesivir for COVID-19 treatment emphasizes the importance of an individual's genetic makeup in determining the most effective therapeutic plan. Specifically, the metabolic transformation of Remdesivir into its active form relies heavily on Cytochrome P450 enzymes, such as CYP2C8, CYP2D6, and CYP3A4. Genetic polymorphisms can result in variations in these enzymes, subsequently affecting how the drug is metabolized. This alteration can influence the effectiveness of the drug and its side effects. By identifying an individual as a poor, intermediate, extensive, or ultrarapid metabolizer, which is determined by their specific P450 alleles, healthcare professionals can personalize dosing strategies. This approach aims to optimize drug effectiveness and minimize adverse reactions, truly embodying the principle of precision medicine.¹⁹⁵ In addition to minimizing adverse events through precision strategies, there also exists the potential to decrease the occurrence of disease-related complications. Understanding risk factors and stratification of patients based on pre-existing comorbidities such as obesity, cardiovascular diseases, arterial hypertension, type 2 diabetes mellitus, and immunosuppression allows better management of the inflammatory responses and cytokine storm induced by SARS-CoV-2.¹⁹⁶

Efficiency in resource allocation, cost savings and cost-effectiveness: The use of advanced genomics and proteomics technologies enabled the rapid cloning and expression of SARS-CoV-2 viral proteins, which aided the development of inexpensive,

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- 191 Radin, J. M., Quer, G., Ramos, E., Baca-Motes, K., Gadaleta, M., Topol, E. J., & Steinhubl, S. R. (2021). Assessment of Prolonged Physiological and Behavioral Changes Associated With COVID-19 Infection. *JAMA Network Open*, 4(7), e2115959. <https://doi.org/10.1001/jamanetworkopen.2021.15959>
- 192 Smartphone apps in the COVID-19 pandemic | *Nature Biotechnology*. (n.d.). Retrieved October 11, 2022, from <https://www.nature.com/articles/s41587-022-01350-x>
- 193 Miller, D. J., Capodilupo, J. V., Lastella, M., Sargent, C., Roach, G. D., Lee, V. H., & Capodilupo, E. R. (2020). Analyzing changes in respiratory rate to predict the risk of COVID-19 infection. *PloS One*, 15(12), e0243693. <https://doi.org/10.1371/journal.pone.0243693>
- 194 Kermali, M., Khalsa, R. K., Pillai, K., Ismail, Z., & Harky, A. (2020). The role of biomarkers in diagnosis of COVID-19—A systematic review. *Life sciences*, 254, 117788.
- 195 Franczyk, B., Rysz, J., Miłośki, J., Konecki, T., Rysz-Górzyńska, M., & Gluba-Brzózka, A. (2022). Will the use of pharmacogenetics improve treatment efficiency in COVID-19?. *Pharmaceuticals*, 15(6), 739.
- 196 Traversi, D., Pulliero, A., Izzotti, A., Franchitti, E., Iacoviello, L., Gianfagna, F., Gialluisi, A., Izzì, B., Agodi, A., Barchitta, M., Calabrò, G. E., Hoxhaj, I., Sassano, M., Sbrogiò, L. G., Del Sole, A., Marchiori, F., Pitini, E., Migliara, G., Marzuillo, C., ... Boccia, S. (2021). Precision Medicine and Public Health: New Challenges for Effective and Sustainable Health. *Journal of Personalized Medicine*, 11(2), 135. <https://doi.org/10.3390/jpm11020135>

rapid diagnostic tests for detecting COVID-19.^{197,198} Identifying variants that might be a public health concern led to better resource management and targeting scarce resources towards these variants. For example, in England, potential vaccine-escape variants of SARS-CoV-2 were detected using community-based testing.¹⁹⁹ In addition, contact tracing together with mass testing campaigns, were shown to diminish the burden on healthcare systems and increase the recovery of patients by facilitating rapid access to healthcare.²⁰⁰

Improved efficacy and overall survival (OS): The use of machine learning algorithms was shown to improve the survival of COVID-19 patients by identification of responders of corticosteroid or remdesivir treatment.²⁰¹ In the early stages of the pandemic, advanced genomic and proteomic analyses allowed researchers to understand the mechanisms of viral entry and molecular interactions with hosts that determine the spread of the virus. Upon a better understanding of viral genome and cell entry mechanisms, spike proteins were identified as the main therapeutic targets to prevent the virus's entry and further spread. Both genomics and proteomics enabled the rapid understanding of viral protein function and pathogenesis, as well as the identification of virus-specific factors and potential targets for drug design.²⁰² In addition, researchers used artificial intelligence tools and big data from genetic databanks to expedite the discovery of vaccines and therapeutics.²⁰³

A recent literature review and meta-analysis on the real-world effectiveness of COVID-19 vaccines indicated strong protection across various metrics. For fully vaccinated individuals, the vaccines were found to be 89.1% effective against infection, 97.2% effective against hospitalization, 97.4% effective against intensive care unit admission, and 99.0% effective against death due to SARS-CoV-2. The vaccines also demonstrated considerable preventive efficacy against infection among the general population aged 16

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- 197 Saravanan, K. A., Panigrahi, M., Kumar, H., Rajawat, D., Nayak, S. S., Bhushan, B., & Dutt, T. (2022). Role of genomics in combating COVID-19 pandemic. *Gene*, 823, 146387. <https://doi.org/10.1016/j.gene.2022.146387>
- 198 Dopazo, J., Maya-Miles, D., García, F., Lorusso, N., Calleja, M. Á., Pareja, M. J., López-Miranda, J., Rodríguez-Baño, J., Padillo, J., Túnez, I., & Romero-Gómez, M. (2021). Implementing Personalized Medicine in COVID-19 in Andalusia: An Opportunity to Transform the Healthcare System. *Journal of Personalized Medicine*, 11(6), Article 6. <https://doi.org/10.3390/jpm11060475>
- 199 The impact of genomics on precision public health: Beyond the pandemic | *Genome Medicine* | Full Text. (n.d.). Retrieved October 11, 2022, from <https://genomemedicine.biomedcentral.com/articles/10.1186/s13073-021-00886-y>
- 200 Yalaman A, Basbug G, Elgin C, Galvani AP. Cross-country evidence on the association between contact tracing and COVID-19 case fatality rates. *Sci Rep*. 2021;11(1):2145. Published 2021 Jan 25. doi:10.1038/s41598-020-78760-x
- 201 Lam, C., Siefkas, A., Zelin, N. S., Barnes, G., Dellinger, R. P., Vincent, J.-L., Braden, G., Burdick, H., Hoffman, J., Calvert, J., Mao, Q., & Das, R. (2021). Machine Learning as a Precision-Medicine Approach to Prescribing COVID-19 Pharmacotherapy with Remdesivir or Corticosteroids. *Clinical Therapeutics*, 43(5), 871–885. <https://doi.org/10.1016/j.clinthera.2021.03.016>
- 202 Saravanan, K. A., Panigrahi, M., Kumar, H., Rajawat, D., Nayak, S. S., Bhushan, B., & Dutt, T. (2022). Role of genomics in combating COVID-19 pandemic. *Gene*, 823, 146387. <https://doi.org/10.1016/j.gene.2022.146387>
- 203 Nascimento, I. J. B. do, Marcolino, M. S., Abdulazeem, H. M., Weerasekara, I., Azzopardi-Muscat, N., Gonçalves, M. A., & Novillo-Ortiz, D. (2021). Impact of Big Data Analytics on People's Health: Overview of Systematic Reviews and Recommendations for Future Studies. *Journal of Medical Internet Research*, 23(4), e27275. <https://doi.org/10.2196/27275>

and older (86.1%), among the elderly (83.8%), and among healthcare workers (95.3%).²⁰⁴ According to a scientific report by the World Health Organization (WHO), COVID-19 vaccines have saved over a million lives in Europe since the end of 2020.²⁰⁵

Improved patient management: Identification of risk factors for developing severe COVID-19 was critical to find the right care pathways for patients during the COVID-19 pandemic. A multi-disciplinary panel of scientists in Germany used a 27-item survey to assess each patient's individual risk of developing severe COVID-19 and secondary infections. Each patient received personalised recommendations for testing, vaccination, self-isolation and treatment using the estimated risk score.²⁰⁶ Other factors such as temperature, ventilatory ratio and/or mechanical ventilation power trajectory allowed prediction of mortality, excessive inflammatory response and best-care pathway for each patient.²⁰⁷

As a broader application of risk factor identification, investigation of genome sequences from patients in different geographical areas showed the association between the ABO blood types and COVID-19 severity patterns and allowed healthcare practitioners to identify patients with increased risk for hospitalisation, mechanical ventilation, renal replacement therapy, and prolonged ICU admission.²⁰⁸

Improved socio-economic value (productivity): Mass testing using genomic sequencing has allowed countries to better manage quarantine and control the spread of COVID-19 by providing more accurate and timely information about the virus's transmission patterns.²⁰⁹ By analyzing the genetic makeup of the virus, scientists can identify and track new variants, understand how the virus is spreading, and identify potential hotspots or clusters. This information could inform decisions about quarantine measures, travel restrictions, and public health interventions, allowing countries to better manage the pandemic while minimizing disruptions to daily life and economic activity. Additionally, mass testing has enabled individuals to safely return to work and other activities by identifying asymptomatic carriers of the virus and taking appropriate measures to prevent its spread, thereby increasing productivity while minimizing the risk of outbreaks.

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- 204 Zheng, C., Shao, W., Chen, X., Zhang, B., Wang, G., & Zhang, W. (2022). Real-world effectiveness of COVID-19 vaccines: a literature review and meta-analysis. *International Journal of Infectious Diseases*, 114, 252-260.
- 205 JB, M. M., Mook, P., Smallwood, C., & Pebody, R. (2023). Estimated number of deaths directly averted as a result of COVID-19 vaccination. *Abstrakt vom*, 17.
- 206 Thieme, A. H., Gertler, M., Mittermaier, M., Gröschel, M. I., Chen, J. H., Piening, B., Benzler, J., Habenicht, D., Budach, V., & Gevaert, O. (2022). A web-based app to provide personalized recommendations for COVID-19. *Nature Medicine*, 28(6), Article 6. <https://doi.org/10.1038/s41591-022-01797-0>
- 207 Annane, D., & Meduri, G. U. (2022). Precision medicine for corticotherapy in COVID-19. *Intensive Care Medicine*, 48(7), 926–929. <https://doi.org/10.1007/s00134-022-06751-9>
- 208 Traversi, D., Pulliero, A., Izzotti, A., Franchitti, E., Iacoviello, L., Gianfagna, F., Gialluisi, A., Izzì, B., Agodi, A., Barchitta, M., Calabrò, G. E., Hoxhaj, I., Sassano, M., Sbrogiò, L. G., Del Sole, A., Marchiori, F., Pitini, E., Migliara, G., Marzuillo, C., ... Boccia, S. (2021). Precision Medicine and Public Health: New Challenges for Effective and Sustainable Health. *Journal of Personalized Medicine*, 11(2), 135. <https://doi.org/10.3390/jpm11020135>
- 209 Robishaw JD, Alter SM, Solano JJ, Shih RD, DeMets DL, Maki DG, Hennekens CH. Genomic surveillance to combat COVID-19: challenges and opportunities. *Lancet Microbe*. 2021 Sep;2(9):e481-e484. doi: 10.1016/S2666-5247(21)00121-X. Epub 2021 Jul 27. PMID: 34337584; PMCID: PMC8315763.

The study from the UK showed that a voluntary mass testing pilot program, known as Covid-SMART, for asymptomatic individuals, resulted in a 25% reduction in COVID-19 related hospital admissions in Liverpool. This reduction was even higher (43%) during the first month of the program when it was assisted by the military.²¹⁰ In addition to mass testing, contact tracing together with mass testing campaigns were shown to diminish the burden on healthcare systems and increase the recovery of patients by facilitating rapid access to healthcare.²¹¹ In Catalonia (Spain), the economic impact of widespread workplace testing strategies for COVID-19, employing both PCR and RAT tests, meant savings in social costs of €10.44 per test or €5575.49 per positive case identified. Around 38% of this amount represents savings from efficient healthcare resource usage, including hospital and ICU beds and monitoring infected cases. The remaining 62% stems from improved health outcomes by preventing disease and death. In situations with higher infection rates and more significant strain on health resources, these figures could escalate by a factor of ten to €130.24 per test and €69,565.59 per positive case.²¹²

Driving innovation system: Overall, more than 70% of the COVID-19 vaccines were developed using genomic methodologies.²¹³ The availability of the virus's genomic information as well as advancements in genome editing technologies, allowed researchers to rapidly develop new vaccines using modern techniques such as mRNA-based vaccines, DNA-based, protein subunit or recombinant viral vector vaccines. Precision vaccinology also allowed the development of variant-specific vaccines, such as the omicron-specific vaccine. In the UK, the identification of the omicron variant and its unique transmission dynamics led to the rapid implementation of the booster programme.²¹⁴

Key role of precision health (PH) and precision medicine (PM) and metrics to assess its level of adoption in COVID-19

In the case of COVID-19, the use of advanced genomic and proteomic approaches facilitated a better understanding of the disease for improved surveillance, prevention and rapid development of vaccines as well as therapeutics. Widespread use of genomic sequencing allowed the identification of viral mutations and different variants; therefore, countries were able to adapt their responses to the COVID-19 pandemic and implement suitable prevention measures as needed. Therefore, in Chapter 3, we evaluated selected countries based on the use of genomic sequencing to identify circulating variants of COVID-19 virus in the country for prevention and monitoring of the disease.

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- 210 Zhang, X., Barr, B., Green, M., Hughes, D., Ashton, M., Charalampopoulos, D., ... & Buchan, I. (2022). Impact of community asymptomatic rapid antigen testing on covid-19 related hospital admissions: synthetic control study. *bmj*, 379.
- 211 Yalaman A, Basbug G, Elgin C, Galvani AP. Cross-country evidence on the association between contact tracing and COVID-19 case fatality rates. *Sci Rep*. 2021;11(1):2145. Published 2021 Jan 25. doi:10.1038/s41598-020-78760-x
- 212 López Seguí, F., Navarrete Duran, J. M., Tuldrà, A., Sarquella, M., Revollo, B., Llibre, J. M., ... & Such Faro, P. (2021). Impact of mass workplace COVID-19 rapid testing on health and healthcare resource savings. *International Journal of Environmental Research and Public Health*, 18(13), 7129.
- 213 Saravanan, K. A., Panigrahi, M., Kumar, H., Rajawat, D., Nayak, S. S., Bhushan, B., & Dutt, T. (2022). Role of genomics in combating COVID-19 pandemic. *Gene*, 823, 146387. <https://doi.org/10.1016/j.gene.2022.146387>
- 214 How COVID-19 transformed genomics and changed the handling of disease outbreaks forever. (n.d.). Retrieved October 11, 2022, from <https://www.gavi.org/vaccineswork/how-covid-19-transformed-genomics-and-changed-handling-disease-outbreaks-forever>

3. Disparities in the adoption of precision health (PH) and precision medicine (PM) approaches across selected countries

Chapter 3 assesses the differences in the adoption of PH/PM approaches across selected EU countries (Denmark, Estonia, France, Germany, Poland, and Spain) and England. We analyze the use of PH/PM in specific types of cancer, familial hypercholesterolemia (FH), type 1 diabetes mellitus (T1DM), and COVID-19. To assess the uptake of PH/PM approaches across these disease areas, we selected the most relevant metric in the application of PH/PM approaches in each disease area as this differs across disease areas and patient care pathway. Our metrics for oncology include market access and reimbursement for precision therapies, companion diagnostics, and contributing factors to access delays. We evaluate the existence of screening programs and the availability of genetic testing for FH patients. For type 1 DM, we examine access to continuous glucose monitoring technologies. For COVID-19, we explore the use of genomic sequencing to identify circulating variants. This chapter provides insights into the disparities in precision medicine adoption and highlights areas for improvement.

3.1. Disparities in the adoption of precision health (PH) and precision medicine (PM) approaches for breast and lung cancer in selected countries

Since the adoption of any health technology requires market access authorisation and agreement to reimburse, our analysis aimed to identify differences in time to market (TTM). This is the lag between marketing authorisation by the European Medicines Agency (EMA) and national reimbursement decisions. It is noted that TTM does not necessarily translate to patient uptake (use of health technology by patients), but TTM is a critical precursor to patient access while also a good metric for comparing adoption levels in countries. In this analysis, only newly approved targeted therapies by EMA between 2017 – 2021 were included to ensure focus on new PM-driven innovations. Reimbursement decision dates available on NAVLIN were used to determine TTM for selected targeted therapies in focus countries, as shown in Table 6.

Table 6: Reimbursement decision dates for selected targeted therapies

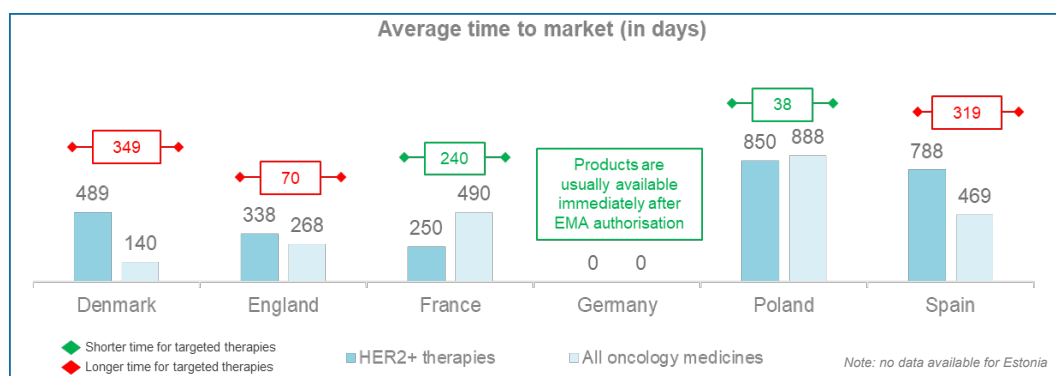
Targeted therapy	EMA approval date	Country (reimbursement decision date)						
		Denmark	England	Estonia	France	Germany	Poland	Spain
HER2								
Enhertu	2021-01-18	NR	2021-05-26	***	2021-06-16	NA	***	NR
Tukysa	2021-02-11	2022-03-23	2022-04-27	***	2021-06-02	NA	***	NR
Nerlynx	2018-08-31	2021-03-11	2019-11-20	***	NR	NA	2020-10-12	2022-07-28
EGFR								
Rybrevent	2021-12-09	***	NR	***	NR	NA	***	***
Vizimpro	2019-04-02	NR	2019-08-14	***	2019-10-23	NA	NR	2020-10-21
Tagrisso	2018-06-07	2019-06-13	2020-10-14	***	2020-03-20	NA	2022-05-10	2019-06-13
Key Trastuzumab deruxtecan [fam-trastuzumab deruxtecan] (Enhertu) Tucatinib (Tukysa) Neratinib (Nerlynx) Amivantamab (Rybrevent) Dacomitinib (Vizimpro) Osimertinib (Tagrisso)						*** – data not available NR – not reimbursed NA – not applicable (access granted after EMA approval)		

Data source: NAVLIN

Further, the assessment entailed a comparison of average TTM between selected targeted therapies and general oncology medicines approved within the same period (2017 – 2021) to see whether countries are prioritising PH/PM-driven innovations (Figure 8 and Figure 10).

The analysis found wide variation in TTM for targeted therapies in focus countries based on available data on EMA approvals and reimbursement decisions in countries in scope. Between 2017 and 2021, EMA approved three targeted therapies for HER2 - neratinib (2018), trastuzumab deruxtecan (2021), and tucatinib (2021), and three targeted therapies for EGFR - osimertinib (2018), dacomitinib (2019) and amivantamab (2021). For HER2, England and Germany reimburse all three HER2 therapies. Denmark reimburses two newly approved HER2 therapies (neratinib and tucatinib) while France also reimburses two (trastuzumab deruxtecan and tucatinib). Based on available data, Poland and Spain reimburse only one newly approved HER2 (neratinib) within the period. In Germany, health technologies, including PH/PM oncology medicines, are usually available immediately after EMA authorisation.

Figure 8: TTM for HER2 targeted therapies and general oncology medicines



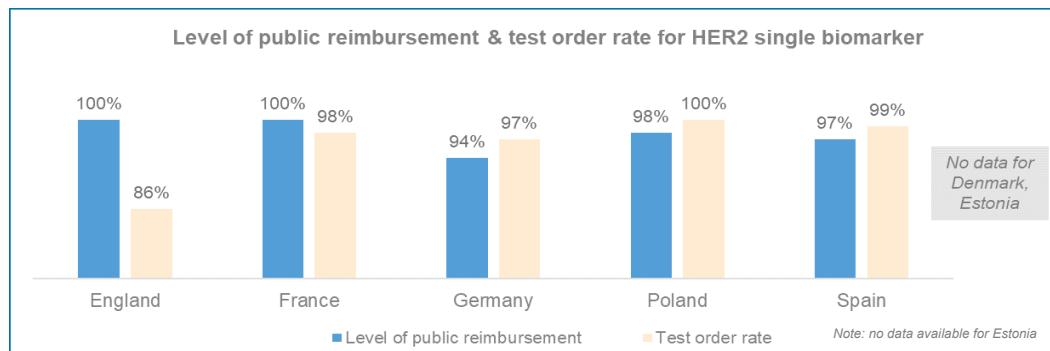
Source: CRA analysis of EFPIA W.A.I.T. Indicator survey 2021 and NAVLIN data (2022)

From the analysis, TTM for targeted therapies varies across countries. There are also notable differences between TTM for targeted therapies and general oncology medicines, which also vary by country. Generally, the average TTM for selected HER2 therapies in countries in scope is 504 days²¹⁵, longer than that of all oncology medicines at 393 days²¹⁶. Only France and Poland have shorter TTM for newer HER2 therapies (240 and 38 days, respectively), although Poland has the longest TTM for both targeted therapies and all oncology medicines (Figure 9). In France, TTM for targeted therapies is shorter than that of all oncology medicines perhaps due to the impact of its early access scheme (Autorisation Temporaire d'Utilisation, ATU).

²¹⁵ Publicly available data from respective national reimbursement bodies

²¹⁶ Based on data from EFPIA W.A.I.T. Indicator survey 2021

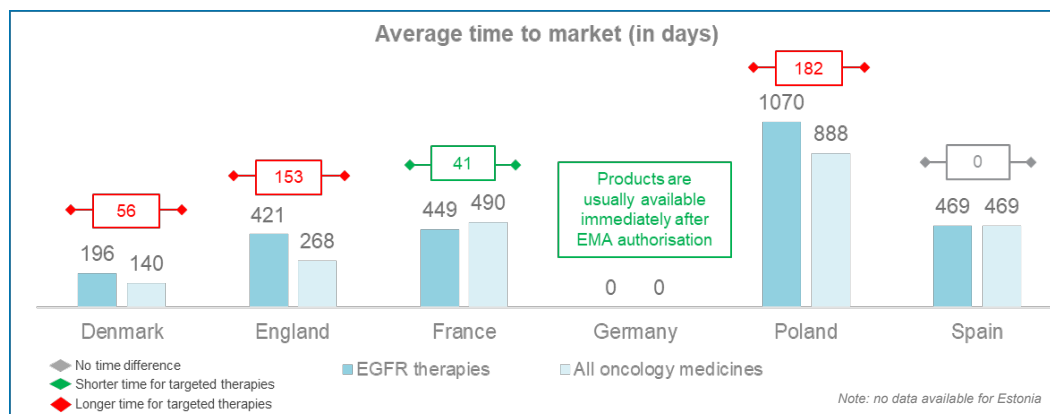
Figure 9: Level of public reimbursement and test order rate for HER2 single biomarker



Source: Normanno et al. (2022)

For HER2 biomarker, the level of public reimbursement and test order rate²¹⁷ is high (>90%) in all countries where data is available. As shown in Figure 9, the level of public reimbursement varies from 94% in Germany²¹⁸ to 100% in England and France.²¹⁹

Figure 10: TTM for EGFR targeted therapies and general oncology medicines



Source: CRA analysis of EFPIA W.A.I.T. Indicator survey 2021 and NAVLIN data (2022)

For EGFR targeted therapies, only osimertinib is reimbursed in all countries in scope except Estonia where data was not available as of the time of analysis. Average TTM is generally longer for EGFR therapies at 469 days²²⁰ than for all oncology medicines, 393 days²²¹. Only France has a shorter TTM for (41 days) compared to all oncology medicines (Figure 10).

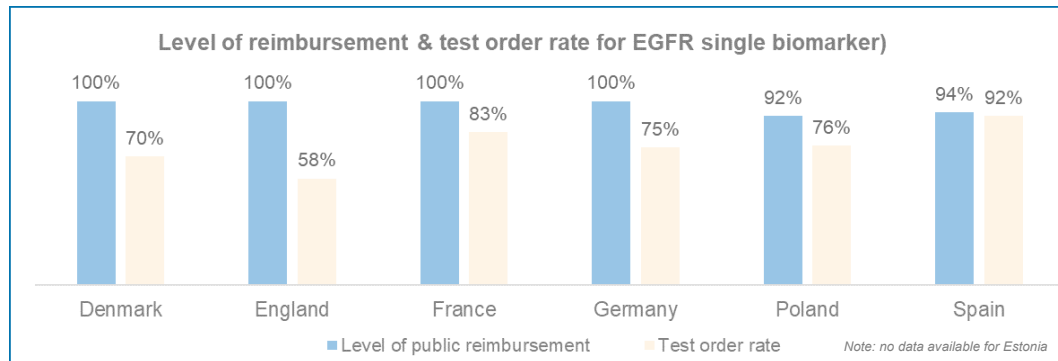
217 Test order rate is defined as percentage share of total unique biopsies for which a given biomarker test was performed.

218 The remaining 6% reimbursement is covered by the pharmaceutical companies.

219 Normanno, N., Apostolidis, K., Wolf, A., Dieri, R. A., Deans, Z., Fairley, J., Maas, J., Martinez, A., Moch, H., Nielsen, S., Pilz, T., Rouleau, E., Patton, S., & Williams, V. (2022). Access and quality of biomarker testing for precision oncology in Europe. *European Journal of Cancer*, 176, 70–77. <https://doi.org/10.1016/j.ejca.2022.09.005>

220 Publicly available data from respective national reimbursement bodies

221 Based on data from EFPIA W.A.I.T. Indicator survey 2021

Figure 11: Level of public reimbursement level and test order rate for EGFR single biomarker

Source: Normanno et al. (2022)

For EGFR biomarker testing, the level of public reimbursement was high across all countries, but test order rates were not as high. The test order rate ranges from 58% to 92% (Figure 11). The test order rate for EGFR is much lower than that of HER2 across all countries in scope where data is available. This may partly be because HER2 diagnostics have been around much longer than EGFR.

Overall, the results of the comparative analysis showed notable differences in access to targeted therapies and companion diagnostics across countries. From available data, the average TTM is longer for newer targeted therapies than for all oncology medicines. Time to market appears to be shorter in England, France and Germany than in other countries in scope. Early access schemes in countries like France and England have shown to facilitate faster access to targeted therapies.^{222,223} Reimbursement policy in Germany in which reimbursement of medicines is allowed immediately following EU market authorisation has been found to generally facilitate faster access to health technologies.²²⁴

Based on analyses from other studies, we identified 10 enablers of faster time to patient access, including factors that could facilitate shorter TTM and faster patient uptake (Figure 12).

222 Balasubramanian, G., Morampudi, S., Chhabra, P., Gowda, A., & Zomorodi, B. (2016). An overview of Compassionate Use Programs in the European Union member states. *Intractable & rare diseases research*, 5(4), 244–254. <https://doi.org/10.5582/irdr.2016.01054>

223 Office for Life Sciences. Gov.uk (2016). Guidance on Early access to medicines scheme (EAMS): task group and principles. Available at: <https://www.gov.uk/government/publications/early-access-to-medicines-scheme-eamshow-the-scheme-works/early-access-to-medicines-scheme-eams-task-group-and-principles>

224 Detiček, A., Locatelli, I., & Kos, M. (2018). Patient Access to Medicines for Rare Diseases in European Countries. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*, 21(5), 553–560. <https://doi.org/10.1016/j.jval.2018.01.007>

Figure 12: Enablers of faster access to precision cancer therapeutics and diagnostics



Source: CRA analysis of EFPIA (2022)²²⁵, Uyl-de Groot et al. (2020), Vintura (2020)²²⁶

** P&R Pricing and Reimbursement

Using selected indicators (Table 7) for each enablers of faster access (Figure 12), our analysis identified good practices that drive faster access to precision cancer diagnostics and therapeutics across countries in scope. The summary analysis is presented in Table 7, and the detailed analysis is in Annex 5.8.

225 EFPIA (2022). The root cause of unavailability and delay to innovative medicines. Developed by Charles River Associates. Available at: <https://www.efpia.eu/media/636822/root-cause-unavailability-delays-cra-report-april-2022-final.pdf>

226 Vintura (2020). Every day counts: Improving time to patient access to innovative oncology therapies in Europe. Available at: https://www.vintura.com/wp-content/uploads/2020/08/White-paper-every-day-counts-improving-time-to-patient-access-to-innovative-oncology-therapies-in-europe_from-EFPIA_and_Vintura.pdf

Table 7: Comparative analysis of enablers of faster access to innovative cancer medicines

Enablers of faster access to innovative therapies	Indicator/data source	Denmark	England	Estonia	France	Germany	Poland	Spain
Early access programmes	Early access schemes	High	High	Low	High	High	Low	High
Initiation of P&R process	Early start & less use of ERP	Medium	High	Low	Medium	High	Low	Medium
Speed of national timelines and adherence	Median time from HTA submission to recommendation	Medium	Medium	Low	High	High	Low	High
Alignment on evidence requirement	HTA acceptance of surrogate endpoints	Medium	Medium	Low	Medium	Medium	Medium	Medium
Alignment on value and price	Use of both financial outcome MEAs	Medium	High	High	High	Low	High	Medium
Value assigned to product differential and choice	Product availability within ATC4 therapeutic classes	High	High	High	Medium	High	Low	Medium
Budget to implement decisions	GDP per capita	High	High	Medium	High	High	Medium	High
Diagnosis, supporting infrastructure & relevance to patients	Level of reimbursement of companion diagnostics & TORs	High	High	Medium	High	High	Low*	High
Minimal layers of decision-making process	Little or no variation between national & regional processes	High	High	High	High	High	Low	Medium
Reimbursement of targeted therapies	# of reimbursed targeted treatments for HER2+ breast cancer and PD-L1 NSCLC**	Medium	High	Low	High	High	Medium	Medium
Summary of access index		Medium	High	Low	High	High	Low	Medium

Source: CRA analysis of various sources

Key: ERP – external reference pricing; HTA – health technology assessment; MEA – managed entry agreement; ATC4 – anatomical therapeutic chemical classification 4; GDP – gross domestic product; TOR – test order rate

The analysis in Table 7 provides a summary of access index in which Denmark, England, Germany and France have high access index based on their implementation of many good practices for enabling faster access to PH/PM innovations.

In order to take full advantage of the value of PH/PM in addressing population health needs in cancer care, policy implications of the ten enablers of faster access to PH/PM innovations described above need to be factored into regional and national cancer response in Europe. The regulation on health technology assessment for joint clinical assessment²²⁷ and Europe's Beating Cancer Plan, launched in February 2021, are good examples of ongoing regional initiatives that address some of the issues propagating delays to PH/PM innovations in cancer care in Europe. In particular, Europe's Beating Cancer Plan recognises the value of PH/PM approaches in cancer care and aims, amongst other interventions, to promote the adoption of PH/PM approaches in cancer care and reduce disparities in the uptake of these approaches across Europe.

The findings from the analysis of enablers of faster access to PH/PM innovations in cancer care can inform the implementation of Europe's Beating Cancer Plan by prioritising early access schemes, streamlining decision-making processes, and increasing investments in diagnostics and supporting infrastructure. Policymakers can improve access to innovative medicines and reduce disparities in cancer care across Europe. As the EU finalises plans to roll out the new Partnership on Personalised Medicine under Horizon Europe as part of Europe Cancer Mission, it is important that considerations around the ten enablers of faster access to PH/PM innovations are factored into the design and implementation of that initiative.

In addition to the imminent implementation of the EU HTA regulation, which entails joint clinical assessment and scientific consultations with standard procedures and methodologies across the EU²²⁸, policy initiatives at national levels should consider early initiation of the pricing and reimbursement process and compliance with stipulated timelines is crucial to ensure equitable access to innovative therapies across Europe.

Investments in diagnostics and supporting infrastructure, such as NGS technology for biomarker testing, are essential to enable targeted therapies and improve cancer outcomes. Streamlining decision-making processes and increasing the speed of uptake at the provider level will be essential in achieving the goals of Europe's Beating Cancer Plan.

3.2. Disparities in the adoption of precision health (PH) and precision medicine (PM) approaches for familial hypercholesterolaemia (FH) in selected countries

FH, a condition that remains largely underdiagnosed, is a prime example of where precision medicine can make a major impact on public health. In Europe, 90% of those living with FH are unaware of their condition.²²⁹ The lack of universal paediatric screening programs

227 Regulation (EU) 2021/2282. Available at: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32021R2282>

228 Implementation of the Regulation on health technology assessment. Published June 15, 2023. Accessed June 19, 2023. https://health.ec.europa.eu/health-technology-assessment/regulation-health-technology-assessment/implementation-regulation-health-technology-assessment_en

229 <https://fheurope.org/latest-news/fh-paediatric-screening-in-europe/>

across all countries remains a major barrier to early diagnosis and the full potential of precision approaches, specifically genetic testing.

Our analysis of selected countries highlights that genetic testing for FH is available and covered by health insurance in most cases. But the challenge lies in identifying patients who could benefit from such testing. This underutilisation of genetic testing is reflected in the low to medium-range utilisation rates observed in all the selected countries (Table 8).

Table 8: Overview of FH screening in selected countries

	Denmark	England	Estonia	France	Germany	Poland	Spain
Universal screening program	No	Pilot programs	Pilot programs	No	Pilot programs	No	No
Screening Type implemented	Cascade screening	Cascade screening	Cascade screening & Universal screening (pilot)	Cascade screening	Cascade screening & Universal screening (pilot)	Cascade screening	Cascade screening
Targeted population	Children of all ages, adults	Adults and children above 10 years	Children of all ages, adults	Children of all ages, adults	Lower Saxony - Children (2-6 years) Bavaria - Children (5 -14 years)	Children (at some institutions), Adults	Adults and children above 15 years
Method <small>(TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol)</small>	TC, LDL-C, genetic testing	TC, LDL-C, genetic testing	LDL-C; sometimes followed by genetic testing	TC, LDL-C, genetic testing	TC, LDL-C, genetic testing	TC, LDL-C, genetic testing	TC, LDL-C, genetic testing
Identified FH	<20%	<8%	<5%	No data	No data	No data	6%
Genetic testing funded	Yes	Yes	Limited	Yes	Yes	Limited	Limited
Utilisation of genetic testing for FH	Medium	Medium	Low	Low	Medium	Low	Low

Source: CRA analysis of various sources²³⁰

All countries within our scope have implemented cascade testing, albeit in an opportunistic manner rather than through a systematic approach. Despite this, testing first-degree relatives of individuals with suspected familial hypercholesterolemia (FH) through cascade testing has proven to be highly cost-effective, yielding significant improvements in quality of life and increased survival rates for those affected by the condition.

In our analysis, rather than comparing countries, we focus on exploring two countries as case studies to showcase best practices. England and Germany serve as examples of the potential impact of implementing universal paediatric screening programs, and we will delve into their approaches to FH genetic testing and cascade screening to illustrate the benefits that can be achieved through PH/PM (Box 1 and Box 2). Both countries are exploring the options of implementing universal paediatric screening programs, showcasing the positive impact such programs can have on population health. These

230

CRA leveraged findings for all countries from two articles 1) Vallejo-Vaz, Antonio J., et al. "Overview of the current status of familial hypercholesterolaemia care in over 60 countries-The EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC)." *Atherosclerosis* 277 (2018): 234-255. 2) Wilemon, Katherine A., et al. "Reducing the clinical and public health burden of familial hypercholesterolemia: a global call to action." *JAMA cardiology* 5.2 (2020): 217-229.

Denmark: Svendsen, Karianne, et al. "Genetic testing is essential for initiating statin therapy in children with familial hypercholesterolemia: examples from Scandinavia." *Atherosclerosis* 316 (2021): 48-52.; Hedegaard, B. S., et al. "A Danish nationwide study of individuals suspected of FH referred from general practice to lipid clinics: Clinical characteristics, plasma lipoprotein (a) and final diagnosis." *Atherosclerosis* 355 (2022): 144.

England: Child-family screening for familial hypercholesterolemia: ethical issues (<https://www.gov.uk/government/publications/child-family-screening-for-familial-hypercholesterolemia-ethical-issues/child-family-screening-for-familial-hypercholesterolemia-ethical-issues>), National Health Service (NHS). (2021). Familial hypercholesterolemia (FH) (<https://www.england.nhs.uk/london/london-clinical-networks/our-networks/cardiac/familial-hypercholesterolaemia/>), British Heart Foundation. (2021). Familial hypercholesterolaemia (FH) (<https://www.bhf.org.uk/informationsupport/conditions/familial-hypercholesterolaemia#:~:text=FH%20is%20an%20inherited%20condition,in%20your%20blood%20remains%20high.>)

Estonia: Alver, Maris, et al. "Recall by genotype and cascade screening for familial hypercholesterolemia in a population-based biobank from Estonia." *Genetics in Medicine* 21.5 (2019): 1173-1180.,

France: Rabès, Jean-Pierre, Sophie Béliard, and Alain Carrié. "Familial hypercholesterolemia: experience from France." *Current Opinion in Lipidology* 29.2 (2018): 65-71., Ferrières, Jean, et al. "Screening and treatment of familial hypercholesterolemia in a French sample of ambulatory care patients: A retrospective longitudinal cohort study." *PLoS One* 16.8 (2021): e0255345.

Germany: Sanin, Veronika, et al. "Population-based screening in children for early diagnosis and treatment of familial hypercholesterolemia: design of the VRONI study." *European Journal of Public Health* 32.3 (2022): 422-428., Kordonouri, Olga, et al. "New approach for detection of LDL-hypercholesterolemia in the pediatric population: the Fr1dolin-Trial in Lower Saxony, Germany." *Atherosclerosis* 280 (2019): 85-91., Genetic Testing in the Context of Familial Hypercholesterolaemia Management - HTA Austria – Austrian Institute for Health Technology Assessment GmbH (https://eprints.aihta.at/1281EPR/1/HTA-Projektbericht_Nr.130.pdf)

Spain: Mata, Pedro, et al. "Diagnosis and treatment of familial hypercholesterolemia in Spain: consensus document." *Atencion primaria* 47.1 (2014): 56-65., Arrobas Velilla, Teresa, Ángel Brea, and Pedro Valdivielso. "Implementation of a biochemical, clinical, and genetic screening programme for familial hypercholesterolemia in 26 centres in Spain: The ARIAN study." *Frontiers in Genetics* (2022): 2312.

programs aim to provide a precise genetic diagnosis and improve risk stratification, leading to better management, prevention and the recruitment of affected relatives through cascade screening.

Box 1: Case Study England

In England, the National Health Service (NHS) has implemented a long-term plan to tackle FH, recognizing the importance of early diagnosis and effective treatment of the condition.²³¹ In the UK, the 2019 NHS long-term plan aims to increase the proportion of those identified as having heterozygous FH from 7% in 2021 to 25% over 5 years.²³² The 2017 NICE FH guideline has recommended case finding in primary care using electronic records as an acceptable and highly cost-effective method for individual practices to identify patients who so far did not have the benefit of treatment.

As part of the NHS long-term plan, England has launched several screening programs aimed at identifying individuals with FH and providing them with the necessary treatment. One of these programs is the cascade screening program, which involves testing first-degree relatives of individuals diagnosed with FH. This approach has proven to be highly cost-effective and has the potential to significantly improve quality of life and survival rates among individuals with FH.²³³ Genetic testing for FH has been available in the NHS for some time and is an exemplar of how genomic technologies are being embedded into routine care in the NHS.²³⁴

In addition to the cascade screening program, England has also launched child-parent screening programs, such as the Academic Health Science Network (AHSN) program. This program offers genetic testing to children aged 10-12 who have a family history of heart disease or elevated cholesterol levels. This early identification of individuals with FH enables them to make lifestyle changes and start treatment early, reducing their risk of heart disease and other complications. The Child-Parent Screening Program for FH is currently being piloted for 24 months across 7 academic health science networks (AHSNs) and will be completed in 2023.²³⁵

The implementation of these screening programs and the utilising genetic testing in England has contributed to an increase in the number of individuals diagnosed with FH, providing them with the necessary treatment and improving their overall health outcomes. In conclusion, England's commitment to the early detection and effective

231 NHS England Familial Hypercholesterolemia (FH) <https://www.england.nhs.uk/london/london-clinical-networks/our-networks/cardiac/familial-hypercholesterolaemia/>

232 <https://www.gov.uk/government/publications/child-family-screening-for-familial-hypercholesterolemia-ethical-issues/child-family-screening-for-familial-hypercholesterolemia-ethical-issues>

233 NICE Familial hypercholesterolaemia: identification and management Clinical Guideline [CG71] <https://www.nice.org.uk/guidance/cg71>

234 Gidding, S. S., Wiegman, A., Grosej, U., Freiburger, T., Peretti, N., Dharmayat, K. I., Daccord, M., Bedlington, N., Sikonja, J., Ray, K. K., Santos, R. D., Halle, M., Tokgözoğlu, L., Gutiérrez-Ibarluzea, I., Pinto, F. J., & Geanta, M. (2022). Paediatric familial hypercholesterolaemia screening in Europe: public policy background and recommendations. *European journal of preventive cardiology*, 29(18), 2301–2311. <https://doi.org/10.1093/eurjpc/zwac200>

235 The AHSN Network - <https://www.ahsnnetwork.com/about-academic-health-science-networks/national-programmes-priorities/lipid-management-and-fh/child-parent-screening#:~:text=Child%2DParent%20Screening%20offers%20a,Care%20heel%20prick%20capillary%20test.>

treatment of FH serves as a model for other countries looking to tackle this condition and improve public health.

Box 2: Case Study Germany

In Germany VRONI screening program was established and funded by the Bavarian State Ministry of Health and Care for FH as a proof-of-concept/pilot study in early 2021²³⁶. It is the first population-based screening program for the early detection of FH associated with genetic mutations in children in Southern Germany and >380 paediatricians are involved in the screening program²³⁷. Around 8100 children were screened by April 2022, and pilot project aims to reach 50,000 children in 2024²³⁸. As a part of the screening program, all children in Bavaria are offered a FH screening test during their preliminary examinations (ages of 5-14 years) or during any other visit to their paediatrician. In conclusion, VRONI is a cutting-edge model of care for familial hypercholesterolemia (FH) that combines scientific research and clinical practice. The primary goal of VRONI is to identify and treat patients with FH through molecular and clinical diagnosis, with a focus on population-based screening in children. The collection and analysis of a large population-based dataset on individuals with FH will provide realistic estimates of the prevalence of FH in Southern Germany. VRONI will also aid in the care and support of FH patients and contribute to the development of FH screening programs. Furthermore, VRONI will address ethical questions related to FH.²³⁹

Paediatric screening programs for familial hypercholesterolaemia (FH) are crucial for preventing cardiovascular disease later in life by measuring cholesterol levels and genetic testing. In recognition of this potential, the International Consortium for Personalised Medicine (ICPerMed) has awarded best practice recognition to the FH project as an area that can greatly benefit from PH/PM approaches.²⁴⁰ While England and Germany have made progress in improving FH screening and applying precision medicine approaches, other countries such as Denmark, Estonia, France, Poland, and Spain still require

236 DigiMed Bayern - <https://www.digimed-bayern.de/en/work-packages/wp3familial-hypercholesterolemia.html>

237 Sanin, V., Schmieder, R., Ates, S., Schlieben, L. D., Wiehler, J., Sun, R., Decker, M., Sander, M., Holdenrieder, S., Kohlmayer, F., Friedmann, A., Mall, V., Feiler, T., Dreßler, A., Strom, T. M., Prokisch, H., Meitinger, T., von Scheidt, M., Koenig, W., Leipold, G., ... DigiMed Bayern Consortium, Bavarian Pediatricians Consortium (2022). Population-based screening in children for early diagnosis and treatment of familial hypercholesterolemia: design of the VRONI study. *European journal of public health*, 32(3), 422–428.

238 <https://www.sueddeutsche.de/bayern/wissenschaft-muenchen-stoffwechselekrankung-bei-kindern-pilotstudie-ermutigend-dpa-urn-newsml-dpa-com-20090101-220427-99-67687>

239 Sanin, V., Schmieder, R., Ates, S., Schlieben, L. D., Wiehler, J., Sun, R., Decker, M., Sander, M., Holdenrieder, S., Kohlmayer, F., Friedmann, A., Mall, V., Feiler, T., Dreßler, A., Strom, T. M., Prokisch, H., Meitinger, T., von Scheidt, M., Koenig, W., Leipold, G., ... DigiMed Bayern Consortium, Bavarian Pediatricians Consortium (2022). Population-based screening in children for early diagnosis and treatment of familial hypercholesterolemia: design of the VRONI study. *European journal of public health*, 32(3), 422–428.

240 ICPerMED - <https://www.icpermed.eu/en/fh-study-880.php>

improvements. The creation of the European Health Union and its funding programs, such as EU4Health and the Innovative Health Initiative, provides a great opportunity to extend systematic paediatric FH screening across Europe. The Prague Declaration, which aims to increase awareness and diagnosis of FH, highlights the importance of these screening programs in improving health outcomes and reducing the financial and human burdens related to preventable cardiovascular disease (CVD). In 2021, the European Commission Public Health Best Practice Portal acknowledged FH paediatric screening as a top practice in the prevention of non-communicable diseases.²⁴¹ Paediatric FH screening, along with subsequent genetic testing and guideline-based treatment, has the potential to dramatically improve the lives of young people with FH and reduce the risk of CVD.

FH is a paradigm for combining the strengths of both public health and PH/PM approaches, such as the use of machine learning to identify patients with high LDL-C using EHR and genetic testing to confirm the diagnosis. It is one of the most tractable conditions to deliver the promised benefits to society.

The policy implications of the challenges associated with identifying and diagnosing familial hypercholesterolemia (FH) are significant. The potential of PH/PM approaches in FH is immense, but the lack of universal screening programs for children across all countries remains a substantial obstacle to unlocking its full potential. Policymakers should consider implementing paediatric screening programs and innovative approaches to genetic testing and cascade screening, as demonstrated by England and Germany, to improve the identification of individuals with FH. Overall, policymakers should recognise the considerable potential that PH/PM approaches can offer in identifying and managing FH by implementing best practices, expanding access to genetic testing and cascade screening, and increasing awareness of FH among healthcare professionals and the general public.

3.3. Disparities in the adoption of precision health (PH) and precision medicine (PM) approaches for type 1 DM in selected countries

In the case of type 1 DM, we focused on the impact of PH/PM in clinical decision support or patient management. Digital diabetes tools such as continuous glucose monitoring (CGM) devices revolutionized the management of diabetes patients and significantly improved patient outcomes by allowing individualized treatment regimens based on monitoring of each patient's glucose levels. According to Digital Diabetes Index published by The Economist Intelligence Unit in 2020, up-to-date reimbursement pathways that recognize the value of digital diabetes tools are major facilitators for the uptake into the healthcare systems and care delivery pathways.²⁴² Therefore, we evaluated the access and reimbursement status of CGM tools in selected countries.

Following the new trends in patient management and increasing use of personalised solutions, all selected countries provide access to continuous glucose monitoring for type 1 DM patients. Continuous glucose monitoring technologies are fully reimbursed in all selected countries except Poland, which only reimburse 70%. In addition, the main

241 European Commission Best Practices Portal, available at: <https://webgate.ec.europa.eu/dyna/bp-portal/best-practice-file/367>

242 The Economist Intelligence Unit 2020, Digital Diabetes Index, available at <https://digitaldiabetesindex.eiu.com/>

differences in access are linked to the eligible population, with significant variations in the target population in selected countries (Table 9). Germany, England and France provide broad reimbursement without any restrictions, even beyond type 1 DM, such as all insulin-dependent patients in Germany. Following these three countries, Spain also provides fairly broad access however uses some restriction criteria based on clinical outcomes (such as the number of hyperglycaemia episodes) or behavioural traits (such as adherence). Other countries limit access to CGM with age restrictions. The age limit is below 18 in Denmark, below 19 in Estonia and below 23 in Poland.

Table 9: Reimbursement and access to continuous glucose monitoring in selected EU countries

Country	Reimbursement Status	Eligible Population	Access Ranking
Germany	Fully Reimbursed	All patients with insulin-dependent diabetes ²⁴³	1
England	Fully Reimbursed	All T1DM patients ²⁴⁴	2
France	Fully Reimbursed	People treated with insulin (at least three injections per day or continuous subcutaneous insulin infusion [CSII]) >4 years old with diabetes—not limited to type 1 diabetes ²⁴⁵	3
Spain	Fully Reimbursed	Initially only paediatric population but later extended into adult patients with type 1 diabetes mellitus and risk of severe hypoglycemia <ul style="list-style-type: none"> • At least one episode of severe hypoglycemia during the previous year or inadvertent hypoglycemia, • Use intensive insulin therapy (multiple daily doses or insulin pump), • Require at least six digital punctures a day for self-monitoring of blood glucose • Show adequate motivation to maintain good adherence to the device ²⁴⁶ 	4

243 <https://www.ajmc.com/view/neutral-findings-predominate-german-study-of-cgm-use>

244 <https://www.nice.org.uk/news/article/thousands-of-people-with-diabetes-set-to-benefit-from-real-time-information-after-updated-nice-recommendations#:~:text=New%20guidance%20from%20NICE%20has,their%20current%20blood%20glucose%20level>

245 Roussel, R., Riveline, J. P., Vicaut, E., de Pouvourville, G., Detournay, B., Emery, C., Levrat-Guillen, F., & Guerci, B. (2021). Important Drop in Rate of Acute Diabetes Complications in People With Type 1 or Type 2 Diabetes After Initiation of Flash Glucose Monitoring in France: The RELIEF Study. *Diabetes care*, 44(6), 1368–1376. <https://doi.org/10.2337/dc20-1690>

246 <https://mtrconsult.com/news/real-time-continuous-glucose-monitoring-be-included-common-package-benefits-spain>

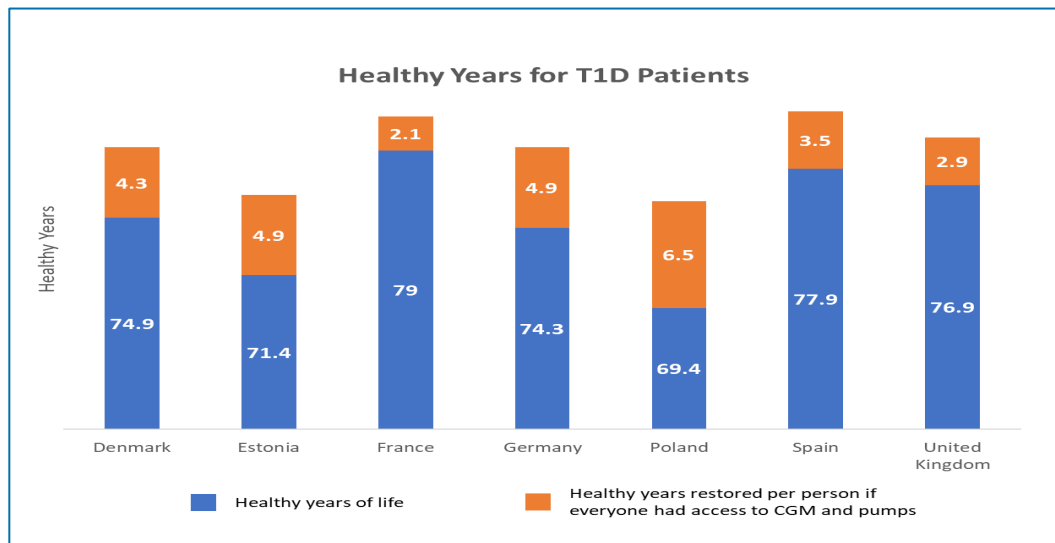
Estonia	Fully Reimbursed	Only under 19 years of age ²⁴⁷	5
Denmark	Fully Reimbursed	Only under 18 years of age <ul style="list-style-type: none"> • HbA1c \geq 70 mM • 1 serious hypoglycemia latest year ²⁴⁸ 	6
Poland	70% Reimbursed	Individuals under the age of 26 years with type 1 diabetes and hypoglycaemia ²⁴⁹	7

As shown in Table 12, all selected countries provide access to CGM tools to some extent with varying levels of the covered population. T1D index further estimated additional healthy years restored per person if everyone in the country had access to CGM and insulin pumps (Figure 13). In line with the reimbursement levels shown in Table 12, countries with limited coverage, such as Poland and Estonia had higher potential healthy years restored compared to the rest of the countries. Countries with broader access mostly had higher currently healthy years of life and lower potential healthy years restored. However, as expected, we did not observe a direct correlation between reimbursement ranking and current or potential healthy years restored, confirming that several other factors influence patient-related outcomes. It is also crucial to highlight that reimbursement or market access, does not guarantee patient access, and several additional factors such as healthcare system structure and capacity, healthcare practitioner availability, education or willingness to use CGM tools might influence the number of people using CGM tools in each country.

247 <https://www.haigekassa.ee/en/people/medical-devices>

248 Nielsen, I. R., Priergaard, M. K., & Kofoed-Enevoldsen, A. (2022). Validity of Danish public criteria for providing flash glucose monitoring to participants with type 1 diabetes-An explorative cohort study. *Endocrinology, diabetes & metabolism*, 5(6), e366. <https://doi.org/10.1002/edm2.366>

249 CEDA diabetes https://ceda-diabetes.eu/wp-d8bc7-content/uploads/2021/12/CEDA_Science_DSH2105.pdf

Figure 13: Healthy Years of Life for T1D incidence in selected EU countries²⁵⁰

Source: Type 1 Diabetes Index

With the increasing adoption of continuous glucose monitoring, the next milestone will be widespread use of closed-loop insulin delivery systems to improve type-1 DM patient management further. With the advancements in technology, closed-loop insulin delivery systems are miniaturized and have become wearable devices. Combined with continuous glucose monitoring, these systems would allow each patient to monitor glucose levels and adjust insulin levels using subcutaneous insulin pumps and the input of advanced algorithms²⁵¹. Therefore, each type-1 DM patient would have a unique treatment regimen tailored to his/her needs and profile. With these advancements, patient outcomes are likely to change even more dramatically than the current improvements in support of the positive impact of PH/PM approaches on population health.

The findings suggest that access to continuous glucose monitoring should be expanded, and age limits in certain countries should be reviewed to ensure that all patients who need it can benefit from this technology. Reimbursing the full cost of continuous glucose monitoring in all EU countries could make it more accessible to patients. Policymakers should consider funding research and development of these technologies and facilitate their deployment in clinical practice. This may involve developing guidelines and standards for the use of PH/PM in the management of type 1 DM, including how to use advanced algorithms to tailor treatment to each patient's needs and profile. Additionally, the education of healthcare professionals on the benefits of CGM is crucial to ensure its proper use and maximize its potential for improving patient outcomes. Policymakers should therefore prioritize the development and implementation of educational programs for healthcare professionals to increase awareness and understanding of CGM technology. Such programs should cover topics such as patient selection, device placement, data interpretation, and appropriate use of CGM data in clinical decision-making.

²⁵⁰ Type 1 Diabetes Index - <https://www.t1dindex.org/>

²⁵¹ Templer S. (2022). Closed-Loop Insulin Delivery Systems: Past, Present, and Future Directions. *Frontiers in endocrinology*, 13, 919942. <https://doi.org/10.3389/fendo.2022.919942>

3.4. Disparities in the adoption of precision health (PH) and precision medicine (PM) approaches for COVID-19 in selected countries

In the midst of the COVID-19 pandemic, the impact of the virus on public health has been widespread, necessitating a comprehensive evaluation of the role of precision medicine/health approaches in prevention and screening strategies. The global SARS-CoV-2 genomic surveillance serves as a crucial component of this evaluation. We present our findings on the sequencing intensity and efficiency²⁵² of SARS-CoV-2 genomic surveillance across selected countries and its potential impact on public health.

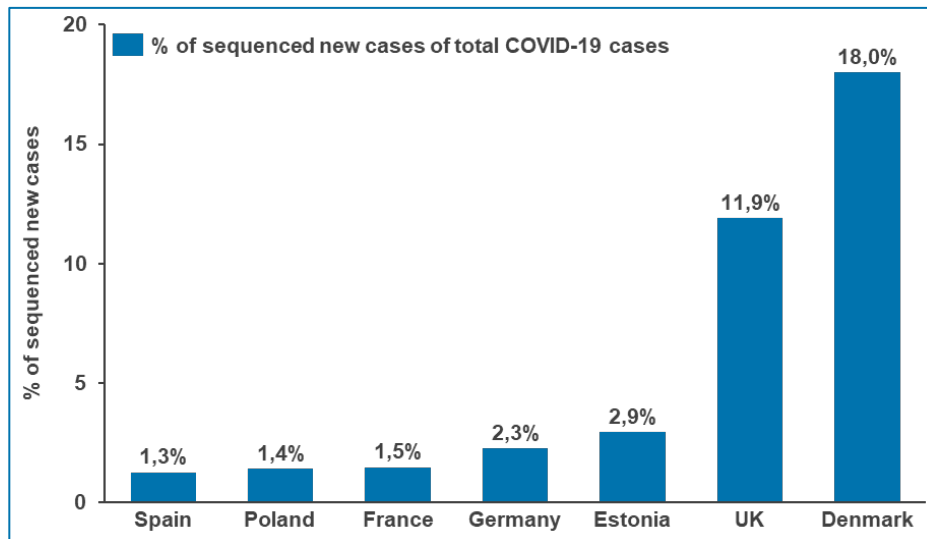
To understand the global SARS-CoV-2 genomic surveillance, we analyzed sequences shared via the Global Initiative on Sharing All Influenza Data (GISAID) to estimate the sequencing intensity and sequencing efficiency across selected countries. Our findings revealed heterogeneity in the availability of SARS-CoV-2 genomic surveillance and sequencing among different countries. Some countries, such as the UK and Denmark, had well-established genomic testing infrastructure and thus performed a higher frequency of routine genomic surveillance (Figure 14). This led to a higher percentage of sequenced COVID-19 cases in these countries, which could have enhanced their prevention policies and strategies. The UK was one of the first countries to implement widespread genomic sequencing of COVID-19 samples, and this information was used to inform decisions on social distancing measures, border control, and vaccine strategy. For instance, the identification of new and highly transmissible variants of the virus led to the implementation of additional measures, including travel restrictions and lockdowns, to curb the spread of these variants and protect public health.²⁵³ On the other hand, some countries, such as Spain and Poland, lagged behind in sequencing, making it more challenging to effectively implement targeted public health measures, track variants, and perform contact tracing.

The number of SARS-CoV-2 sequenced genomes per thousand COVID-19 cases (sequencing efficiency) increased over time in all countries (Figure 15). In an examination of genomic sequencing efficiency for SARS-CoV-2 across 2020 and 2021, a marked improvement was noted in select countries. Poland stood out for achieving a dramatic increase in efficiency, boasting a 32.6-fold enhancement in 2021 compared to the previous year. Germany also demonstrated a commendable increase, albeit more modest, with an 8.5-fold improvement during the same period. Poland and Germany significantly scaled up their pathogen genomic surveillance through investments in infrastructure and human resources. This potentially enabled them to better detect and respond to SARS-CoV-2 variants.

252 Sequencing intensity is defined as % of sequenced new cases of total COVID-19 cases. Sequencing efficiency is defined as the number of SARS-CoV-2 sequenced genomes per thousand COVID-19 cases.

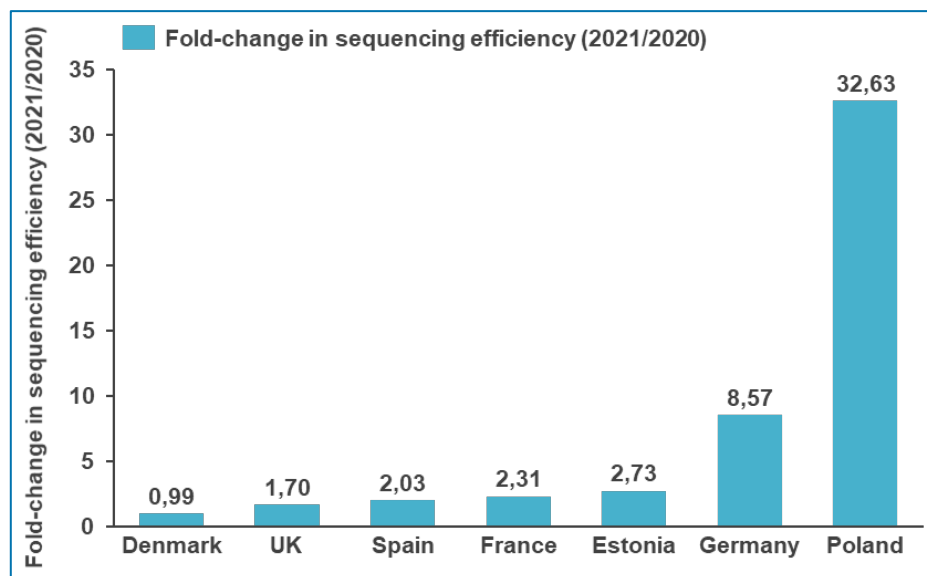
253 UK Government Press Release: UK completes over one million SARS-CoV-2 whole genome sequences, available at <https://www.gov.uk/government/news/uk-completes-over-one-million-sars-cov-2-whole-genome-sequences>

Figure 14: Percentage of sequenced new cases of total COVID-19 cases in selected countries



Source: GISAID EpiCoV database ²⁵⁴

Figure 15: Fold-change in sequencing efficiency (2021/2020) in selected countries



Source: A fold-change in sequencing efficiency use data from Mahanta et al (2022) ²⁵⁵

254 GISAID EpiCoV database (<https://gisaid.org/>) was accessed in November 2022. Data used from March 2020 - October 2022

255 Mahanta U, Saberwal G, Sharma G. Are Countries Becoming Better at SARS-CoV-2 Genomic Surveillance? Front Public Health. 2022 Apr 25;10:887955. doi: 10.3389/fpubh.2022.887955. PMID: 35558539; PMCID: PMC9088876.

The COVID-19 pandemic has emphasized the importance of establishing a robust sequencing infrastructure for effective public health response. Many European countries leveraged advancements in genomic sequencing for screening and prevention during the COVID-19 pandemic and built the necessary infrastructure to mitigate risks for potential future diseases.^{256:257:258:259:260}

In conclusion, global SARS-CoV-2 genomic surveillance plays a vital role in the evaluation of the impact of precision health on public health. The results highlight the heterogeneity in sequencing intensity and efficiency among different countries and the importance of establishing a robust sequencing infrastructure for effective public health response. This infrastructure can also be leveraged to fight antimicrobial resistance, and it is crucial that countries build on the momentum generated during the COVID-19 pandemic to establish their own sequencing infrastructure and ensure a timely and precise local response to sequencing data. To achieve this, countries should work closely with the European Health Emergency Response Authority (HERA) to align their efforts and ensure a coordinated response to public health emergencies.

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- 256 Bager, P., Wohlfahrt, J., Fonager, J., Rasmussen, M., Albertsen, M., Michaelsen, T. Y., ... & Krause, T. G. (2021). Risk of hospitalisation associated with infection with SARS-CoV-2 lineage B. 1.1. 7 in Denmark: an observational cohort study. *The Lancet Infectious Diseases*, 21(11), 1507-1517.
- 257 "Rapid and effective sequencing of SARS-CoV-2 in France" - HAS https://www.has-sante.fr/portail/jcms/c_2980983/en/rapid-and-effective-sequencing-of-sars-cov-2-in-france
- 258 "COVID-19 Genomics UK (COG-UK)" - UK government <https://www.gov.uk/government/collections/covid-19-genomics-uk-cog-uk>
- 259 "Germany's COVID-19 sequencing network" - Robert Koch Institute https://www.rki.de/EN/Content/Institute/Departments/virusgenetics/COVID19Sequencing/COVID19Sequencing_node.html
- 260 "Diagnostic and laboratory support for COVID-19 in Poland" - Polish Ministry of Health <https://www.gov.pl/web/zdrowie/diagnostyka-i-wsparcie-laboratoryjne-w-walce-z-covid-19>

4. Conclusions and policy recommendations

PH/PM has the potential to greatly improve population health outcomes in Europe through better prevention, screening, diagnosis, treatment and patient management. However, for PH/PM to deliver for European patients, some specific policies are important when thinking of therapy areas that address population health needs.

4.1. Policy recommendations to enhance the use of PH/PM approaches in oncology

PH/PM already revolutionize the way we approach cancer care, providing tailored treatments based on an individual's unique genetic makeup and medical history. However, despite its potential, PH/PM has yet to reach its full potential in Europe due mainly to long access delays between countries that negatively impact patients. The EU is at a critical moment, as it must decide whether it wants to remain a leader in innovative precision oncology or fall behind in the global race for progress.

To address this, the revision of the EU Pharmaceutical legislation and the implementation of the EU HTA Regulation in 2025 for oncology products will be key to ensuring equitable access to precision medicine approaches in oncology across Europe. Europe's Beating Cancer plan also presents an opportunity to place patients and citizens at the centre of all decision-making and to address inequalities in access to cancer care across and within EU Member States.

Policy recommendations aim to ensure countries in Europe take full advantage of the benefits of precision approaches in cancer care by enabling faster and wider adoption of precision oncology technologies through smart investments in supporting infrastructure as well as taking best practices in precision approaches to scale across the continent to reduce inequities in access to PH/PM innovations.

Policy recommendations:

- **Addressing inequalities in access to precision oncology:** It is essential to address inequalities in access to precision oncology across and within EU member states to ensure that every patient in Europe has timely access to the care they need. This can be achieved by developing a framework for access to precision oncology in Europe supported by the creation of a system to monitor and report progress across member states.
- **Reducing time to market and access delays:** Timely access to precision technologies is crucial ensuring health systems take full advantage of the benefits of the precision approaches and that patients are able to access innovations they need to improve their health outcomes and quality of life. The EU is already taking steps to institute joint clinical assessment for HTA decisions in Europe. In addition to this effort, the EU should also support countries to implement identified best practices for enabling faster TTM including creating and scaling early access schemes for precision technologies as well as addressing demand-side challenges at the healthcare provider level.
- **Prioritising targeted investments in precision diagnosis:** More investments need to be made in precision diagnosis to ensure a full complement of NGS technology with supporting infrastructure is available in all countries. The EU should support Member States to intensify and sustain investment in genome-based innovations coupled with supportive policies and regulatory environment to

optimise such investments. This can be done by establishing a hub and spoke model for cancer care and creating clear referral pathways to centralised diagnostic facilities to treatment centres.

- **Improving access to biomarkers:** Improving access to biomarkers is essential in unlocking the value of precision cancer care. This can be achieved by developing a framework for using biomarkers in precision oncology and creating a system to monitor and report progress across Member States.
- **Embracing innovative tools:** Utilising new technologies and therapies is crucial in reducing the number of people affected by cancer and in limiting demand on existing services. This can be achieved through investment in R&D and the creation of a policy and regulatory environment that encourages innovation.
- **Fostering world-leading cancer research:** Encouraging investment in R&D is essential in addressing unmet needs in cancer care and in maintaining Europe's position as a leader in the field. Building on the EU's Mission on Cancer objective to upscale innovation for cancer care, the EU should strengthen and sustain investment in the innovation ecosystem, including world-class innovation hubs, high-growth biotech companies, and a supportive policy and regulatory environment.
- **Data sharing and collaboration:** Optimising data sharing among healthcare providers, researchers, and patients can build a robust data ecosystem that supports the development and implementation of precision medicine approaches, providing a more comprehensive understanding of population health needs. This can be achieved through initiatives like the European Healthcare Data Space (EHDS) to establish strong data governance frameworks and define interoperability standards. Data sharing will also enhance uptake of artificial intelligence capabilities for cancer care in Europe.
- **Using artificial intelligence to accelerate the implementation of precision oncology:** The use of artificial intelligence (AI) has the potential to revolutionize the way we approach cancer care, providing faster and more accurate diagnoses and enabling more tailored treatments. The EU should encourage the development of AI-based cancer care solutions and ensure that they are adopted in a responsible and ethical manner.

In conclusion, these policy recommendations aim to ensure that PH/PM approaches in oncology reach their full potential in addressing population health needs in Europe. By embracing innovative tools, fostering world-leading cancer research, placing patients at the centre of care, addressing inequalities in access to care, reducing delays for access to innovative treatments, improving access to quality biomarkers, and using AI to accelerate diagnosis and improve cancer care, the EU can ensure that every patient in Europe has timely access to the care they need.

4.2. Policy recommendations to enhance the use of PH/PM approaches in familial hypercholesterolemia (FH)

Policy recommendations aim to improve the use of genetic testing for familial hypercholesterolaemia (FH) in Europe, leading to early diagnosis, effective treatment, and improved health outcomes for those affected by the condition. The recommendations to improve the use of PH/PM approaches include the following key points:

- **Improving awareness and education of healthcare professionals:** Develop training programs for healthcare professionals to improve their knowledge and skills in identifying and diagnosing FH, as well as implementing PH/PM approaches to diagnosis, treatment and management. Providing healthcare professionals with the knowledge and tools to implement precision medicine approaches can improve patient outcomes, including reducing the risk of cardiovascular disease. This can have a significant impact on population health outcomes by preventing premature deaths and reducing the burden of cardiovascular disease on healthcare systems.
- **Establishing screening programs for children:** Early identification of FH through paediatric screening programs can lead to earlier intervention and management, ultimately reducing the risk of cardiovascular disease and improving population health outcomes. Implementing such programs can help ensure that all children are given the opportunity to receive early intervention and management for FH, reducing health inequalities and improving overall population health outcomes.
- **Building infrastructure for genetic testing:** Invest in building infrastructure for genetic testing to enable the identification of individuals with FH and their families. Building the necessary genetic testing infrastructure can help identify individuals with FH early on, allowing for earlier intervention and management. Furthermore, the implementation of genetic testing infrastructure can help promote research and development in PH/PM, leading to further improvements in population health outcomes.

By following these policy recommendations, Europe can advance towards a future where every individual with FH is diagnosed and treated promptly and accurately, decreasing their chance of developing heart disease and enhancing their overall health outcomes. The utilisation of PH/PM in the screening and management of FH plays a crucial role in this endeavour.

4.3. Policy recommendations to enhance the use of PH/PM approaches in Type 1 DM

Policy recommendations aim to improve the adoption of PH/PM approaches in type 1 DM, leading to improved patient outcomes and quality of life by minimizing the disease burden. The recommendations include the following key points:

- **Establish registries and data infrastructure to generate and capture real-world evidence across health systems:** By establishing local, regional, national, or EU-wide registries, policymakers can demonstrate the efficacy of PH/PM approaches in type-1 DM. Systematic data infrastructure across health systems would facilitate data collection and sharing optimisation. This could enable the creation of more effective treatment plans, reducing hospitalisation rates and improving patient outcomes. By collecting data across different populations, researchers can identify trends and best practices that will allow for the widespread adoption of PH/PM approaches.
- **Educate healthcare practitioners:** By educating healthcare practitioners on the value and benefits of PH/PM approaches, policymakers can ensure widespread adoption and remove one of the key barriers to patient access. This will enable healthcare providers to deliver more personalized treatments tailored to each patient's specific needs, leading to improved outcomes and reduced healthcare costs.

- **Empower patients:** Allowing patients to track key disease parameters related to their disease and enabling self-management with the use of digital tools and PH/PM approaches can improve their quality of life. They can better manage their condition and prevent complications, leading to fewer hospitalizations and improved population health. For example, within the Health Outcomes Observatory project (H2O), individuals with diabetes can utilize digital tools and patient-centric approaches to track their blood glucose levels, medication adherence, and lifestyle factors. This empowers them to better manage their condition, leading to improved quality of life, reduced complications, and ultimately fewer diabetes-related hospitalizations. Supported by the Innovative Medicines Initiative (IMI) and the European pharmaceutical industry through EFPIA, H2O aims to incorporate patients' experiences and preferences, enabling them to remain in control of their data and actively participate in decisions affecting their individual healthcare and the broader patient community.
- **Increase access to PH/PM tools:** Widespread access to PH/PM tools, such as continuous glucose monitoring, can help patients better manage their condition and prevent complications. By extending access to all diabetes patients in all disease stages, policymakers can improve patient outcomes and reduce healthcare costs associated with hospitalizations and other complications.
- **Ensure equitable access:** PH/PM approaches should not be contingent on specific behavioural traits or characteristics. Access to these approaches should be based on standardized eligibility criteria that are impartial and objective, ensuring fair and equal access for all individuals. Policymakers can ensure equitable access to these tools, regardless of demographics or socio-economic status, to reduce disparities in health outcomes and promote population health.

Overall, the policy recommendations for improving the adoption of PH/PM approaches in type 1 DM have the potential to significantly improve population health outcomes by reducing the disease burden associated with type 1 DM. By generating real-world evidence, educating healthcare practitioners and patients, providing widespread access to PH/PM tools, and ensuring equitable access, policymakers can unlock the full potential of PH/PM approaches in improving health outcomes and reducing the burden of type 1 DM on populations.

4.4. Policy recommendations to enhance the use of PH/PM approaches in COVID-19

Based on the findings presented in this report, it is recommended that the EU Member States (at least countries in the scope) take action to support the application of PH/PM approaches, specifically focusing on genomic sequencing. The recommendations include the following key points:

- **Establishing a robust sequencing infrastructure:** By establishing a robust sequencing infrastructure for effective public health response across all EU Member States, policymakers can improve population health outcomes by enabling timely and accurate identification of infectious disease outbreaks, including emerging variants. This can help prevent disease spread, reduce morbidity and mortality, and minimize the economic burden on healthcare systems.
- **Utilising the increased awareness of genomic sequencing among healthcare professionals:** Encouraging the use of genomic sequencing in the prevention and screening of other diseases can improve health outcomes by enabling early

identification and intervention of diseases, reducing the burden of treatment, and improving patient outcomes. Leveraging the increased capacity and workforce developed during the COVID-19 pandemic to support the use of genomic sequencing for other diseases can further accelerate the adoption of PH/PM approaches and improve population health outcomes.

- ***Integrating genomic sequencing with other relevant health data:*** Incorporating genomic sequencing data with demographic, clinical, and environmental data can provide a more comprehensive understanding of public health, leading to improved disease prevention and management. This can also facilitate the development of more effective precision medicine approaches tailored to individual patients, improving health outcomes and reducing healthcare costs.
- ***Addressing Antimicrobial Resistance (AMR):*** Recognising genomic sequencing as part of the solution to tackle AMR and building on existing initiatives such as the EU Health Emergency Preparedness and Response Authority (HERA) and the Innovative Health Initiative (IHI) to establish a common framework for the sequencing of SARS-CoV-2 and other infectious diseases can improve population health outcomes by enabling the development of more effective treatments and reducing the spread of resistant infections. Leveraging the infrastructure and capacity built during the COVID-19 pandemic to support the use of genomic sequencing for other diseases can further accelerate the adoption of precision medicine approaches to address AMR and improve population health outcomes.

4.5. General policy recommendations

There are a number of recommendations not specific to therapy areas that are critical to important in upscaling PH/PM approach to address population health needs in Europe. These include:

- ***Prioritising availability and investment in PH/PM technologies:*** Investing in PH/PM technologies like genomic sequencing and targeted therapies can ensure that patients have access to the most advanced and beneficial health technologies, leading to better prevention, screening, diagnosis, treatment, and patient management. By ensuring availability and investment in these technologies, Europe can remain a leader in healthcare innovation, which can help address population health needs. This is important for all disease areas considered in this report. We find that PH/PM technologies can improve patient outcomes, increase efficiency in healthcare delivery, and lead to better resource allocation, which can significantly impact the overall sustainability and effectiveness of the healthcare system.
- ***Data sharing and collaboration:*** Prioritising data sharing and collaboration among healthcare providers, researchers, and patients can build a robust data ecosystem that supports the development and implementation of PH/PM approaches, providing a more comprehensive understanding of population health needs. Data sharing was particularly important during the COVID-19 pandemic, but it is also important for cancer and type 1 DM research. By leveraging initiatives like the European Healthcare Data Space (EHDS), Europe can improve disease prevention and management and promote medical research, ultimately improving population health outcomes.
- ***Education and training of healthcare providers:*** By prioritising education and training for healthcare providers on PH/PM approaches, including interpretation of

genomic data and the use of advanced technologies like machine learning and artificial intelligence, Europe can ensure that healthcare providers have the necessary skills and knowledge to address the population healthcare needs. For oncology, it is important that healthcare providers are educated on the benefits of PH/PM approaches. Europe's Beating Cancer Plan can be leveraged to develop and implement training programs for healthcare providers, specifically focused on PH/PM approaches. For FH and type 1 DM, improved education will help identify and diagnose patients and implement PH/PM approaches to treatment and management. Raised awareness of the general public and healthcare providers on the benefits of genomic sequencing during COVID-19 could have a spillover effect in other disease areas.

- **Ensure equal access to PH/PM approaches:** It is crucial to ensure that all patients have access to the best possible care through PH/PM approaches, including targeted therapies and diagnostics, without any inequalities in patient access to medicines and diagnostics across Europe. To achieve this, pricing and reimbursement (P&R) policies must be aligned with the value delivered by innovations. In addition, P&R policies should evolve to reflect advances in precision approaches. A disconnect between therapy reimbursement and of their companion diagnostics also contributes to patient access delays. Hence P&R policies should also seek to address this challenge. By prioritising value-based P&R policies with minimal or no time delay to reimbursement decision, patients could have timely access to novel PH/PM interventions, thereby contributing to improvement in population health outcomes across Europe. In the report, we observed inequalities in cancer care regarding access to targeted therapies, precision diagnostics, and access to continuous glucose monitoring (CGM) in type 1 DM.
- **Patient-centred care plans:** Developing patient-centred care plans tailored to individual needs and circumstances through PH/PM approaches can promote individualized and more effective treatments, ultimately contributing to the overall improvement of population health outcomes. The report finds that PH/PM approaches are integral to establishing patient-centred care plans, especially in cancers and type 1 DM, as precision approaches provide value along the whole patient care pathway in these diseases. By utilising data sharing and collaboration among healthcare providers, researchers, and patients, Europe can develop patient-centred care plans that take into account a patient's unique genetic and environmental factors, leading to more effective treatment outcomes and improved allocation of health resources.
- **Building infrastructure and raising awareness:** Building infrastructure for PH/PM approaches like genetic testing and genomic sequencing and raising awareness of the benefits of these approaches in disease prevention and surveillance can improve disease detection and prevention before symptoms appear, ultimately improving population health outcomes. By prioritizing the building of a robust infrastructure for precision medicine approaches and raising awareness of the benefits of these approaches in disease prevention and surveillance, Europe can encourage greater uptake and use of these approaches.

By embracing these policy recommendations, Europe has the opportunity to establish itself as a leader in the advancement and application of PH/PM approaches to address the complex healthcare requirements of populations at large. Integral to this effort is the establishment of a robust data infrastructure, the promotion of data sharing, and the

development of digital tools. These elements are crucial enablers of PH/PM, and they are fundamental to enhancing the efficiency, equity, health outcomes, value-for-money, and financial sustainability of health systems. With a focus on preventive measures, diagnosis, treatment strategies, and patient management techniques, Europe can elevate the standard of healthcare delivery and achieve substantial improvements in the health outcomes of its citizens.

5. Annexes

5.1. Glossary

Artificial intelligence	The simulation of human intelligence in machines that are programmed to think like humans and mimic their actions. The term may also be applied to any machine that exhibits traits associated with a human mind such as learning and problem-solving.
Autoantibody	An antibody produced by an organism in response to a constituent of its own tissues.
Bioinformatics	The science of collecting and analysing complex biological data such as genetic codes
Biomarker	A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease.
Biopsy	An examination of tissue removed from a living body to discover the presence, cause, or extent of a disease.
Cancer	A new and abnormal growth of tissue in a part of the body, especially as a characteristic of cancer.
Companion diagnostic	<p>A device which is essential for the safe and effective use of a corresponding medicinal product to:</p> <ul style="list-style-type: none">a) identify, before and/or during treatment, patients who are most likely to benefit from the corresponding medicinal product; orb) identify, before and/or during treatment, patients likely to be at increased risk of serious adverse reactions as a result of treatment with the corresponding medicinal product” <p><i>IVD Regulation 2017/746/EU, Article 2(7)</i></p>
Diagnostic test	A type of test used to help diagnose a disease or condition.
DNA	A biological molecule that carries a person's genetic code.
Exome	The part of the genome that consists of exons, a segment of a DNA or RNA molecule containing information coding for a protein or peptide sequence.
Gene expression profiling	In the field of molecular biology, gene expression profiling is the measurement of the activity of thousands of genes at once, to create a global picture of cellular function.
Genetic testing	The process of analysing cells or tissues to look for genetic changes as a result of heredity.
Genetics	Genetics is the study of heredity. It scrutinizes the functioning and composition of the single gene.
Genomic testing	The process of analysing cells or tissues to identify genetic changes that occur within a cell either due to an internal cause (such as random molecular change within a cell) or an

	external cause (such as tobacco use or sun exposure), which may be a sign of a disease or condition such as cancer.
Genomics	The study of the complete set of DNA (including all of its genes) in a person or other organism. It is the study of genes and their functions, and related techniques.
Germline mutation	A germline mutation, or germinal mutation, is any detectable variation within a germ cell (reproductive cell). A mutation in a sperm or oocyte, when they come together to form a zygote, is passed on to the offspring.
Hyperglycaemia	An excess of glucose in the bloodstream.
Hypoglycaemia	Deficiency of glucose in the bloodstream.
Immunotherapy	The prevention or treatment of disease with substances that stimulate the immune response.
Machine learning	The concept that computer programs can automatically learn from and adapt to new data without being assisted by humans. Deep learning techniques enable this automatic learning through the absorption of huge amounts of unstructured data such as text, images, or video.
Messenger RNA (mRNA)	The form of RNA in which genetic information transcribed from DNA as a sequence of bases is transferred to a ribosome.
Metabolomics	The scientific study of chemical processes involving metabolites, the small molecule substrates, intermediates, and products of cell metabolism.
Molecular diagnostics	A collection of techniques used to analyse biological markers in the genome and proteome – the individual's genetic code and how their cells express their genes as proteins – by applying molecular biology to medical testing.
Next-generation sequencing	An umbrella term used to describe a number of different modern DNA sequencing technologies that use a high-throughput method to determine a portion of the nucleotide sequence of an individual's genome.
Oncogene	A gene involved in normal cell growth, mutations of which are regularly associated with tumorigenic transformation.
PCR	Polymerase chain reaction. A procedure that produces millions of copies of a short segment of DNA through repeated cycles of: (1) denaturation, (2) annealing, and (3) elongation.
Personalised medicine	Personalised medicine is about tailoring medical diagnostics and treatments to individual patient needs based on available evidence and consideration of circumstances and clinical resources
Pharmacogenomic	Relating to the interaction between genetic predisposition and responses to therapeutic drugs.
Precision health	Precision health uses extensive population-specific data to provide the right intervention to the right population at the right

	time. It is a wider concept but complementary concept to precision medicine.
Precision medicine	Precision medicine is defined as a healthcare approach that utilises molecular information (genomic, transcriptomic, proteomic, metabolomic, etc), phenotypic and health data from patients to generate care insights to prevent or treat human disease resulting in improved health outcomes.
Protein expression	The production of proteins by cells. The study of protein expression in cancer cells may give information about a specific type of cancer, the best treatment to use, and how well a treatment works.
Proteomics	The large-scale study of proteomes, a set of proteins produced in an organism, system, or biological context.
Transcriptomics	The study of the complete set of RNA transcripts that are produced by the genome using high-throughput methods.

5.2. Additional information on literature review

For the review, we started by collecting industry commissioned reports and other relevant papers from academia and public agencies (Table 2). We then searched through existing literature including published journal papers, articles and opinion papers, government reports and public policy documents using PubMed and Google search. Keywords used for literature search included “precision medicine”, “precision health”, “personalised medicine”, “population health”, “value”, “benefit”, “enablers”, “prevention”, “screening”, “diagnostics”, “biomarkers”, “therapeutics”, “treatment”, “patient management”, “clinical decision support”, “precision oncology”, “precision vaccinology”, “familial hypercholesterolaemia”, “type 1 diabetes mellitus”, and “COVID-19”, “risk”, “harm”, “cost”, “savings”, “overall survival”, “clinical benefit”. Table 2 summarises the different categories of body of literature reviewed.

Table 10: Summary of papers and resources reviewed

Type	Number	Examples
Academic articles	157	<ul style="list-style-type: none"> Grossman, D. C., Larson, E. B., & Sox, H. C. (2020). Integrating Personalised Medicine With Population Health Management: The Path Forward. <i>JAMA</i>, 324(7), 631–632. https://doi.org/10.1001/jama.2020.1406 Loomans-Kropp, H. A., & Umar, A. (2019). Cancer prevention and screening: The next step in the era of precision medicine. <i>Npj Precision Oncology</i>, 3(1), Article 1. https://doi.org/10.1038/s41698-018-0075-9
Industry published or commissioned reports	12	<ul style="list-style-type: none"> IQN Path, ECPC, EFPIA (2021); Unlocking the potential of precision medicine in Europe – Improving cancer care through broader access to quality biomarker testing LSE (2020); Gill, J., Fontrier, A. M., Miracolo, A., & Kanavos, P.; Access to personalised oncology in Europe
Public agency reports,	26	<ul style="list-style-type: none"> NICE (2015) Diabetes (type 1 and type 2) in children and young people: diagnosis and management.

announcements, news		<ul style="list-style-type: none"> NHS England. Personalised medicine, available at: https://www.england.nhs.uk/healthcare-science/personalisedmedicine/
Other: Public news, Patient Advocacy Groups websites, statistics, product leaflets etc.	31	<ul style="list-style-type: none"> Type 1 Diabetes Index FH Europe - https://fheurope.org/latest-news/fh-paediatric-screening-in-europe/

Source: CRA analysis

5.3. Additional information on external interview programme

Table 11: External interviews conducted by CRA

Disease area	Country	Stakeholder type
Cancer	England	Life sciences expert
	Germany	Patient advocate
	Ireland	Precision medicine advocate
	Denmark	Precision medicine advocate
	Romania	Precision medicine advocate
FH	EU	Patient advocacy group
	England	Academic (Cardiovascular Genetics)
	EU	FH expert
T1D	EU	Academic
	EU	Patient Advocacy Group
Covid-19	England	Academic
	England	Academic

5.4. Examples of precision health(PH) and precision medicine (PM) approaches in selected cancer types along patient care pathway

Prevention: One of the key examples of the use of PH/PM approaches is in cancer screening programmes. For breast and colorectal cancers, predictive genetic tests such as BRCA 1 and 2 are utilised for breast cancer screening.²⁶¹ Testing for PALB2 gene is also used as a predictive tool in breast cancer prevention approaches.²⁶² For colorectal cancer prevention, Epi proColon 2.0 CE, a molecular cancer screening test that detects methylated

²⁶¹ Population-scale DNA test paves way to personalised medicine | Research and Innovation. (n.d.). Retrieved October 10, 2022, from <https://ec.europa.eu/research-and-innovation/en/projects/success-stories/all/population-scale-dna-test-paves-way-personalised-medicine>

²⁶² Harris, E. E. R. (2018). Precision Medicine for Breast Cancer: The Paths to Truly Individualized Diagnosis and Treatment. *International Journal of Breast Cancer*, 2018, 4809183. <https://doi.org/10.1155/2018/4809183>

Septin 9 DNA in blood, is now being used as an alternative to colonoscopy for colorectal cancer screening.²⁶³

Another form of PH/PM approach for cancer prevention is the use of a neoantigen vaccine in patients with Lynch syndrome, which is the commonest cause of hereditary colorectal cancer.^{264,265} Similarly, vaccines targeted at tumour antigens such as mucin 1 (MUC1) have also been found to have the potential to prevent colorectal cancer.²⁶⁶





Lastly, use of new technologies like agnostic AI models to refine risk-stratification definitions is being used for cancer screening recommendations.²⁶⁷

Diagnosis: Precision cancer diagnostics is one of the most advanced approaches of PH/PM. The use of molecular biomarkers is used across different stages of cancer progression, starting from diagnosis through treatment and monitoring.

Diagnostic approaches (sequencing method) in use include comprehensive genomic profiling (CGP), single assays, targeted panels and exome sequencing. Comprehensive Genomic Profiling (CGP) covers all cancer biomarkers and provides a comprehensive assessment of immune-oncology biomarkers used in cancer care. Single-gene assays are limited to a single biomarker. Targeted panel cover specific genes but not the entire coding sequence. Whole-exome sequencing covers the entire coding sequence. Examples of pan-cancer biomarkers include NTRK1, NTRK2, NTRK3, microsatellite instability (MSI) and tumour mutation burden (TMB). Specific examples of currently used biomarkers per cancer type is provided in Table 4.

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- 263 Lamb, Y. N., & Dhillon, S. (2017). Epi proColon® 2.0 CE: A Blood-Based Screening Test for Colorectal Cancer. *Molecular Diagnosis & Therapy*, 21(2), 225–232. <https://doi.org/10.1007/s40291-017-0259-y>
- 264 National Cancer Institute, Annual Plan and budget Proposal for Fiscal Year 2023; available at: <https://www.cancer.gov/research/annual-plan/scientific-topics/precision-prevention>
- 265 Gebert, J., Gelincik, O., Oezcan-Wahlbrink, M., Marshall, J. D., Hernandez-Sanchez, A., Urban, K., Long, M., Cortes, E., Tosti, E., Katzenmaier, E.-M., Song, Y., Elsaadi, A., Deng, N., Vilar, E., Fuchs, V., Nelius, N., Yuan, Y. P., Ahadova, A., Sei, S., ... Kloor, M. (2021). Recurrent Frameshift Neoantigen Vaccine Elicits Protective Immunity With Reduced Tumor Burden and Improved Overall Survival in a Lynch Syndrome Mouse Model. *Gastroenterology*, 161(4), 1288-1302.e13. <https://doi.org/10.1053/j.gastro.2021.06.073>
- 266 Loomans-Kropp, H. A., & Umar, A. (2019). Cancer prevention and screening: The next step in the era of precision medicine. *Npj Precision Oncology*, 3(1), Article 1. <https://doi.org/10.1038/s41698-018-0075-9>
- 267 Farina, E., Nabhen, J. J., Dacoregio, M. I., Batalini, F., & Moraes, F. Y. (n.d.). An overview of artificial intelligence in oncology. *Future Science OA*, 8(4), FSO787. <https://doi.org/10.2144/fsoa-2021-0074>

Table 12: Some examples of biomarkers for selected cancer types

 Breast	 Lung	 Colon	 AML
AKT1	AKT1	AKT1	FLT3-ITD
AR	ALK	BRAF	KIT
BRCA1	BRAF	HRAS	RAS
BRCA2	DDR2	KRAS	CEBPA
ERBB2	EGFR	MET	RUNX1
FGFR1	ERBB2	MLH1	TP53
FGFR2	FGFR1	MSH2	IDH1/2
PIK3CA	FGFR3	MSH6	NPM1
PTEN	KRAS	NRAS	ASXL1
PALB2	MAP2K1	PIK3CA	BCR-ABL1
HER2	MET	PMS2	FLT3-TKD
PD-L1	NRAS	SMAD4	ZRSR2
	PIK3CA	TP53	EZH2
	PTEN	EGFR	U2AF1
	PD-L1	MSI	SRSF2
	TP53	HER-2	BCOR
	ROS1		
	TMD		
	RET		

Sources: Illumina, El Achi and Kanagal-Shamanna (2021)²⁶⁸

The use of biomarker tests to inform diagnosis, therapeutic decisions and other clinical decision-making has increased significantly in the management of many cancer types.^{269,270}

Another precision diagnostic approach is radiomics method which is used to inform models that can successfully predict treatment response and/or side effects from cancer treatments.²⁷¹

Treatment: Precision therapeutics also known as targeted therapy are medicines designed to attack a specific target on cancer cells.²⁷² Some examples of precision cancer treatments for various cancer types include EGFR inhibitors, mTor inhibitors, P13K inhibitors, PARP inhibitors, kinase inhibitors amongst others.

Patient management and care: Deployment of platforms for sharing genomic data and other data types with the use of data sharing technologies and digital health tools has

268 El Achi, H., & Kanagal-Shamanna, R. (2021). Biomarkers in Acute Myeloid Leukemia: Leveraging Next Generation Sequencing Data for Optimal Therapeutic Strategies. *Frontiers in Oncology*, 11. <https://www.frontiersin.org/articles/10.3389/fonc.2021.748250>

269 Lassen, U. N., Makaroff, L. E., Stenzinger, A., Italiano, A., Vassal, G., Garcia-Foncillas, J., & Avouac, B. (2021). Precision oncology: A clinical and patient perspective. *Future Oncology*, 17(30), 3995–4009. <https://doi.org/10.2217/fon-2021-0688>

270 Liquid biopsy of cancer: A multimodal diagnostic tool in clinical oncology—Raffaele Palmirotta, Domenica Lovero, Paola Cafforio, Claudia Felici, Francesco Mannavola, Eleonora Pellè, Davide Quaresmini, Marco Tucci, Franco Silvestris, 2018. (n.d.). Retrieved October 11, 2022, from <https://journals.sagepub.com/doi/full/10.1177/1758835918794630>

271 Farina, E., Nabhen, J. J., Dacoregio, M. I., Batalini, F., & Moraes, F. Y. (n.d.). An overview of artificial intelligence in oncology. *Future Science OA*, 8(4), FSO787. <https://doi.org/10.2144/fsoa-2021-0074>

272 Immunotherapy and non-oncogene driven cancers are not included in this report.

enabled the advancement of precision patient management. Specific examples include clinical decision support applications such as AACR Project GENIE (Genomics Evidence Neoplasia Information Exchange) and other bioinformatics like Catalogue of Somatic Mutations in Cancer (COSMIC), the cBioPortal for Cancer Genomics, the “My Cancer Genome” tool and the Cancer Genome Atlas (TCGA) amongst others.^{273,274}

Another example is the web-based patient-reported outcomes (PROs) used for symptom monitoring during chemotherapy.²⁷⁵ Furthermore, powerful computational methods and wearable data collection tools enable better patient management.²⁷⁶

5.5. Examples of precision health (PH) and precision medicine (PM) approaches in FH along patient care pathway

Prevention: Adoption of FH screening programmes is still quite low across Europe. It is estimated that less than 10% of adults and 5% of children with FH in Europe have been diagnosed. Diagnosis typically occurs late in life, around 44 years of age.²⁷⁷ The Netherlands was the first country to systematically identify citizens with FH and place those diagnosed on treatment. In Slovenia in 1995, the first attempt at universal screening²⁷⁸ for FH was undertaken by introducing mandatory cholesterol testing at the age of 5. The country now reaches nearly 91% of their population of around 20,000 children each year with universal paediatric FH screening.²⁷⁹

In Germany, the VRONI study was rolled out in 2021 to test the feasibility of population-based screening for FH in children in Bavaria with the aim of using this as a precursor for a national rollout of FH screening infrastructure.²⁸⁰ In addition to screening programs, the

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- 273 Brown, N. A., Aisner, D. L., & Oxnard, G. R. (2018). Precision Medicine in Non–Small Cell Lung Cancer: Current Standards in Pathology and Biomarker Interpretation. *American Society of Clinical Oncology Educational Book*, 38, 708–715. https://doi.org/10.1200/EDBK_209089
- 274 Bertier, G., Carrot-Zhang, J., Ragoussis, V., & Joly, Y. (2016). Integrating precision cancer medicine into healthcare—Policy, practice, and research challenges. *Genome Medicine*, 8(1), 108. <https://doi.org/10.1186/s13073-016-0362-4>
- 275 Denis, F., Basch, E., Septans, A.-L., Bennouna, J., Urban, T., Dueck, A. C., & Letellier, C. (2019). Two-Year Survival Comparing Web-Based Symptom Monitoring vs Routine Surveillance Following Treatment for Lung Cancer. *JAMA*, 321(3), 306–307. <https://doi.org/10.1001/jama.2018.18085>
- 276 National Cancer Institute, Annual Plan and budget Proposal for Fiscal Year 2023; available at: <https://www.cancer.gov/research/annual-plan/scientific-topics/precision-prevention>
- 277 EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). *Lancet*. 2021 Sep 7:S0140-6736(21)01122-3. doi: 10.1016/S0140-6736(21)01122-3. Epub ahead of print. PMID: 34506743
- 278 Universal FH screening programme uses a 3-step approach including (i) total cholesterol measurement; (ii) children with elevated total cholesterol undergo further FH diagnostic testing; (iii) testing of family members of affected children
- 279 The Time is Now: Cardiovascular Disease as an EU Priority. (n.d.). Familial Hypercholesterolaemia (FH) Europe. Retrieved October 11, 2022, from <https://fheurope.org/latest-news/the-time-is-now-cardiovascular-disease-as-an-eu-priority/>
- 280 Sanin, V., Schmieder, R., Ates, S., Schlieben, L. D., Wiehler, J., Sun, R., Decker, M., Sander, M., Holdenrieder, S., Kohlmayer, F., Friedmann, A., Mall, V., Feiler, T., Dreßler, A., Strom, T. M., Prokisch, H., Meitinger, T., von Scheidt, M., Koenig, W., ... the DigiMed Bayern Consortium, B. P. C. (2022). Population-based screening in children for early diagnosis and treatment of familial hypercholesterolemia: Design of the VRONI study. *European Journal of Public Health*, 32(3), 422–428. <https://doi.org/10.1093/eurpub/ckac007>

use of machine learning was implemented to identify patients at risk of developing FH based on basic laboratory information, such as age and the components of the basic lipid profile.²⁸¹

Diagnosis: Genetic testing plays a central role in FH definitive diagnosis, pathway screening and risk stratification.^{282,283,284,285}

Treatment: The use of pharmacogenomics to identify patients with risk of low efficacy of statins helps improve efficacy.²⁸⁶ However, use of pharmacogenetic testing is yet to become a routine part of clinical practice in many healthcare systems.^{287,288} Precision treatments inhibiting PCSK9 are in use for patients with poor response to statins and those having adverse events.²⁸⁹

Patient management and care: The use of pharmacogenomics can prevent adverse events and guide patient treatment and care. For example, genetic testing can identify individuals who have a high risk of experiencing severe side effects from statins, such as myopathy or rhabdomyolysis. By identifying these individuals, healthcare providers can adjust the dosage or choose an alternative medication to reduce the risk of adverse events.²⁹⁰ Additionally, pharmacogenomics can help identify genetic variants associated

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- 281 AACC (2021). Can machine learning improve on our current approaches of screening for, and diagnoses of, Familial Hypercholesterolemia? Available at <https://www.aacc.org/science-and-research/scientific-shorts/2021/can-machine-learning-improve-screening-diagnosis-of-familial-hypercholesterolemia>
- 282 Population-scale DNA test paves way to personalised medicine | Research and Innovation. (n.d.). Retrieved October 10, 2022, from <https://ec.europa.eu/research-and-innovation/en/projects/success-stories/all/population-scale-dna-test-paves-way-personalised-medicine>
- 283 Nordestgaard, B. G., & Benn, M. (2017). Genetic testing for familial hypercholesterolaemia is essential in individuals with high LDL cholesterol: Who does it in the world? *European Heart Journal*, 38(20), 1580–1583. <https://doi.org/10.1093/eurheartj/ehx136>
- 284 Population-scale DNA test paves way to personalised medicine | Research and Innovation. (n.d.). Retrieved October 10, 2022, from <https://ec.europa.eu/research-and-innovation/en/projects/success-stories/all/population-scale-dna-test-paves-way-personalised-medicine>
- 285 Nordestgaard, B. G., & Benn, M. (2017). Genetic testing for familial hypercholesterolaemia is essential in individuals with high LDL cholesterol: Who does it in the world? *European Heart Journal*, 38(20), 1580–1583. <https://doi.org/10.1093/eurheartj/ehx136>
- 286 Chora, J. R., & Bourbon, M. (2021). Pharmacogenomics of statins and familial hypercholesterolemia. *Current Opinion in Lipidology*, 32(2), 96–102. <https://doi.org/10.1097/MOL.0000000000000746>
- 287 Ahangari, N., Doosti, M., Ghayour Mobarhan, M., Sahebkar, A., Ferns, G. A., & Pasdar, A. (n.d.). Personalised medicine in hypercholesterolaemia: The role of pharmacogenetics in statin therapy. *Annals of Medicine*, 52(8), 462–470. <https://doi.org/10.1080/07853890.2020.1800074>
- 288 Tomlinson, B., Lin, C.-H., Chan, P., & Lam, C. W. (2021). Personalized medicine in lipid-modifying therapy. *Personalized Medicine*, 18(2), 185–203. <https://doi.org/10.2217/pme-2020-0110>
- 289 Myers KD, Knowles JW, Staszak D, Shapiro MD, Howard W, Yadava M, et al. Precision screening for familial hypercholesterolaemia: a machine learning study applied to electronic health encounter data. *Lancet Digit Heal*. 2019;
- 290 Cooper-DeHoff, R. M., Niemi, M., Ramsey, L. B., Luzum, J. A., Tarkiainen, E. K., Straka, R. J., ... & Voora, D. (2022). The clinical pharmacogenetics implementation consortium guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and statin-associated musculoskeletal symptoms. *Clinical Pharmacology & Therapeutics*, 111(5), 1007-1021.

with a poor response to a specific medication, which can help guide personalized treatment to improve efficacy and reduce the risk of adverse events.²⁹¹

5.6. Examples of precision health (PH) and precision medicine (PM) approaches in type 1 DM along the patient care pathway

Prevention: One of the key examples of use of PH/PM approaches in T1D is risk prediction algorithms for screening of high risk-individuals. Several risk prediction algorithms or initiatives are in place to better identify individuals with higher type 1 DM risk. For example, INNODIA (Europe)²⁹² and Bart's Oxford (BOX) Family Study²⁹³ programmes screened relatives of type 1 DM patients for risk identification. Use of biomarkers in the form of autoantibodies is another risk identification strategy and allows early interventions.²⁹⁴

Diagnosis: A great example of the use of PM/PH in TD1M is genetic risk scores or biomarker testing for patient identification. Islet autoantibody testing and additional biomarkers, such as serum or urine C-peptide levels can be used to diagnose type 1 DM patients.²⁹⁵ Continuous glucose monitoring also allows the identification of individual glucose patterns and can aid diagnosis and patient stratification.²⁹⁶

Treatment: With continuous glucose monitoring, type 1 DM patients can monitor their unique glucose values, trends and glycemic variability. Using real-time monitoring, each type 1 DM patient receives personalised treatment regimen based on their unique profile. In addition to glucose monitoring, several biomarkers (ICOS, PD-1, TIGIT, KLRG1) have been identified which may assist better selection of suitable immunotherapies for type 1 DM patients.²⁹⁷

Patient management and care: Biomarkers and continuous glucose monitoring also support patient care and management for type 1 DM patients. AI tools and machine learning algorithms are used to improve care based on each patient's unique profile.

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- 291 Hindi, N. N., Alenbawi, J., & Nemer, G. (2021). Pharmacogenomics variability of lipid-lowering therapies in familial hypercholesterolemia. *Journal of Personalized Medicine*, 11(9), 877.
- 292 <https://www.innodia.eu/peoplewith1d/> INNODIA
- 293 <http://www.bristol.ac.uk/translational-health-sciences/research/diabetes/research/box/> Bart's-Oxford (BOX) family study
- 294 Herold KC, Bundy BN, Long SA, et al. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes [published correction appears in *N Engl J Med*. 2020 Feb 6;382(6):586]. *N Engl J Med*. 2019;381(7):603-613. doi:10.1056/NEJMoa1902226
- 295 Carr ALJ, Evans-Molina C, Oram RA. Precision medicine in type 1 diabetes [published online ahead of print, 2022 Aug 22]. *Diabetologia*. 2022;10.1007/s00125-022-05778-3. doi:10.1007/s00125-022-05778-3
- 296 Klonoff DC, Florez JC, German M, Fleming A. The Need for Precision Medicine to be Applied to Diabetes. *J Diabetes Sci Technol*. 2020;14(6):1122-1128. doi:10.1177/1932296819894295
- 297 Deligne C, You S, Mallone R. Personalized Immunotherapies for Type 1 Diabetes: Who, What, When, and How? *J Pers Med*. 2022 Mar 29;12(4):542. doi: 10.3390/jpm12040542. PMID: 35455658; PMCID: PMC9031881.

5.7. Examples of precision health (PH) and precision medicine (PM) approaches in COVID-19 along the patient care pathway

Prevention: Contact tracing with digital technologies was heavily used in several European countries to prevent the spread of COVID-19 during the pandemic. One of the successful examples was the National Health Service (NHS) COVID-19 app in the UK.²⁹⁸ In addition, using advanced genomic technologies, the virus's genomic information was rapidly identified and allowed the development of new vaccines as a prevention strategy.²⁹⁹

Diagnosis: During the COVID-19 pandemic, advanced diagnostic technologies were used for disease/variant identification and more effective public health response. Moreover, advanced sensors or personalised wearable devices were used to continuously track an individual's physiological and behavioral metrics.^{300,301,302}

Treatment: Machine learning algorithms were used to identify treatment responders in COVID-19.³⁰³ In addition, European Union supercomputing centres were used for repurposing of existing treatments that might react to the SARS-CoV-2 virus by comparing digital models of the coronavirus' proteins and matching them against a database of thousands of existing drugs.³⁰⁴

Patient Management and care: Digital tools were used during COVID-19 pandemic to identify individual patient care pathways and optimal disease management based on the unique needs of patients. Several tools, such as a web-based participatory surveillance strategy among healthcare workers from Switzerland³⁰⁵ or the Safer-Covid app³⁰⁶ most

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- 298 Wymant C, Ferretti L, Tsallis D, et al. The epidemiological impact of the NHS COVID-19 app. *Nature*. 2021;594(7863):408-412. doi:10.1038/s41586-021-03606-z
- 299 Saravanan, K. A., Panigrahi, M., Kumar, H., Rajawat, D., Nayak, S. S., Bhushan, B., & Dutt, T. (2022). Role of genomics in combating COVID-19 pandemic. *Gene*, 823, 146387. <https://doi.org/10.1016/j.gene.2022.146387>
- 300 Radin, J. M., Quer, G., Ramos, E., Baca-Motes, K., Gadaleta, M., Topol, E. J., & Steinhubl, S. R. (2021). Assessment of Prolonged Physiological and Behavioral Changes Associated With COVID-19 Infection. *JAMA Network Open*, 4(7), e2115959. <https://doi.org/10.1001/jamanetworkopen.2021.15959>
- 301 Smartphone apps in the COVID-19 pandemic | *Nature Biotechnology*. (n.d.). Retrieved October 11, 2022, from <https://www.nature.com/articles/s41587-022-01350-x>
- 302 Miller, D. J., Capodilupo, J. V., Lastella, M., Sargent, C., Roach, G. D., Lee, V. H., & Capodilupo, E. R. (2020). Analyzing changes in respiratory rate to predict the risk of COVID-19 infection. *PloS One*, 15(12), e0243693. <https://doi.org/10.1371/journal.pone.0243693>
- 303 Lam, C., Siefkas, A., Zelin, N. S., Barnes, G., Dellinger, R. P., Vincent, J.-L., Braden, G., Burdick, H., Hoffman, J., Calvert, J., Mao, Q., & Das, R. (2021). Machine Learning as a Precision-Medicine Approach to Prescribing COVID-19 Pharmacotherapy with Remdesivir or Corticosteroids. *Clinical Therapeutics*, 43(5), 871–885. <https://doi.org/10.1016/j.clinthera.2021.03.016>
- 304 Digital solutions during the pandemic. (n.d.). [Text]. European Commission - European Commission. Retrieved October 11, 2022, from https://ec.europa.eu/info/live-work-travel-eu/coronavirus-response/digital-solutions-during-pandemic_en
- 305 SAFER-COVIDTM | MyDataHelps. (n.d.). CareEvolution. Retrieved October 11, 2022, from <https://careevolution.com/mydatahelps/safer-covid/>
- 306 Leal-Neto, O., Egger, T., Schlegel, M., Flury, D., Sumer, J., Albrich, W., Babouee Flury, B., Kuster, S., Vernazza, P., Kahlert, C., & Kohler, P. (2021). Digital SARS-CoV-2 Detection Among Hospital Employees: Participatory Surveillance Study. *JMIR public health and surveillance*, 7(11), e33576. <https://doi.org/10.2196/33576>

frequently used in the US allowed individual risk assessments and helped users to make informed decisions.

5.8. Analysis of enablers of faster access to precision cancer therapeutics and diagnostics

1. Early access programs: The existence of early access schemes enables patients to access innovative medicines prior to marketing authorisation and pricing and reimbursement decision in some countries. For example, England has the Early Access to Medicines Scheme (EAMS) which facilitates access to medicines free of charge to the National Health Service (NHS) until the full marketing authorisation is granted. In ³⁰⁷ where medicines addressing high unmet need can be granted an “authorisation temporaire d’utilisation” (ATU) prior to receiving a conditional MA. Products under the ATU system are directly available (time to availability = 0).³⁰⁸ In Spain, regional early access scheme is being considered in Catalonia.³⁰⁹ . Though there is no existence of early access schemes in Germany and Denmark, there is no formal requirement for price setting by competent authority before market launch according to EFPIA’s Market Launch and Withdrawal Survey (May 2020).

2. Initiation of pricing and reimbursement (P&R) process: Early start of P&R process with less use of external reference pricing (ERP) has been found to speed up TTM for innovative medicines.³¹⁰ Countries that do not use ERP for pricing and reimbursement decisions like the Germany and England tend to have faster TTM. The EU Transparency Directive (Directive 89/105/EEC) has set 180 days as the maximum timeline for member states to make P&R decisions. In practice this may be much longer due a number of factors including clock stops, ERP and lack of adherence to the directive. In England, the P&R process can start much earlier before market authorisation, whilst in other countries there is a delay even after publication in the EU Journal.³¹¹ In Germany, the temporary period of

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- 307 Balasubramanian, G., Morampudi, S., Chhabra, P., Gowda, A., & Zomorodi, B. (2016). An overview of Compassionate Use Programs in the European Union member states. *Intractable & rare diseases research*, 5(4), 244–254. <https://doi.org/10.5582/irdr.2016.01054>
- 308 Gasol M, Paco N, Guarga L, Bosch JÀ, Pontes C, Obach M. (2022). Early Access to Medicines: Use of Multicriteria Decision Analysis (MCDA) as a Decision Tool in Catalonia (Spain). *Journal of Clinical Medicine*; 11(5):1353. <https://doi.org/10.3390/jcm11051353>
- 309 Gasol M, Paco N, Guarga L, Bosch JÀ, Pontes C, Obach M. (2022). Early Access to Medicines: Use of Multicriteria Decision Analysis (MCDA) as a Decision Tool in Catalonia (Spain). *Journal of Clinical Medicine*; 11(5):1353. <https://doi.org/10.3390/jcm11051353>
- 310 Incze, A., Kaló, Z., Espín, J., Kiss, É., Kessabi, S., & Garrison, L. P. (2022). Assessing the Consequences of External Reference Pricing for Global Access to Medicines and Innovation: Economic Analysis and Policy Implications. *Frontiers in Pharmacology*, 13. <https://www.frontiersin.org/articles/10.3389/fphar.2022.815029>
- 311 Vintura (2020). Improving time to patient access to innovative oncology therapies in Europe. EFPIA. Available at: <https://www.vintura.com/news/white-paper-every-day-counts/>

free pricing enables immediate access to EMA approved medicines which minimises access delays.³¹²

3. Speed of national timelines and adherence: Most European countries have rules on timelines for HTA and reimbursement decision-making but compliance to these rules can be challenging and unpredictable. Delays in TTM may arise when these rules are not adhered to. However, countries like Germany and France that have specific mechanisms to grant full or partial reimbursement from public resources outside HTA decision framework have been found to have shorter TTM to improve patient access.³¹³

4. Alignment on evidence requirement: Acceptance criteria for endpoint surrogacy in HTA decision framework differs across national HTA and reimbursement bodies. This impacts on decision timelines across countries especially with innovative technology with uncertainty on clinical benefits using conventional endpoints. The level of alignment is highest for the use of biomarkers and real-world evidence (RWE) which are “often accepted” by all HTA bodies. The level of alignment is lowest when HTA bodies are asked for acceptance of surrogate endpoints other than progression-free survival (PFS).^{314,315,316} The recent adoption of the legislation for joint European Health Technology Assessment (EU HTA) could help address this challenge in the near future.³¹⁷ By 2025, oncology and advanced therapy medicinal products (ATMPs) will need to be assessed through the EU HTA mechanism.

5. Alignment on value and price: Even if there was an agreement on evidence regarding the value of a health technology assessment, countries would differ on their ability and willingness to pay. While prices may not necessarily affect the speed of market launch, a positive relationship has been found to exist between high-priced markets and

312 Detiček, A., Locatelli, I., & Kos, M. (2018). Patient Access to Medicines for Rare Diseases in European Countries. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*, 21(5), 553–560. <https://doi.org/10.1016/j.jval.2018.01.007>

313 Detiček, A., Locatelli, I., & Kos, M. (2018). Patient Access to Medicines for Rare Diseases in European Countries. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*, 21(5), 553–560. <https://doi.org/10.1016/j.jval.2018.01.007>

314 Ciani, O., Grigore, B., Blommestein, H., de Groot, S., Möllenkamp, M., Rabbe, S., Daubner-Bendes, R., & Taylor, R. S. (2021). Validity of Surrogate Endpoints and Their Impact on Coverage Recommendations: A Retrospective Analysis across International Health Technology Assessment Agencies. *Medical decision making : an international journal of the Society for Medical Decision Making*, 41(4), 439–452. <https://doi.org/10.1177/0272989X21994553>

315 Research, C. for D. E. and. (2022). Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure. FDA. <https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure>

316 BlueMatter (2021). Demonstrating efficacy of via surrogate endpoints. Available at: <https://bluematterconsulting.com/wp-content/uploads/2021/05/Demonstrating-Efficacy-via-Surruogates-May-2021.pdf>

317 Commission proposal on Health Technology Assessment

the availability of medicines.³¹⁸ To minimise the impact of price of medicines on availability and access, use of flexible managed entry agreements (MEA) has been found to enable faster TTM.³¹⁹ Many European countries, including England, France, and Spain, now use MEAs including value-based contracting approaches for innovative and high cost therapeutics to enable faster TTM and patient access.^{320,321}

6. Value assigned to product differential and choice: Generally, countries tend to reimburse more technologies within a therapeutic class as the number of therapeutic options decreases, as seen in IQVIA analysis of a series of ATC4 therapeutic classes.³²² Competition between innovative medicines is encouraged in some countries, with reimbursement of follow-on products in a class, as this can lead to better value for the payer. Non-reimbursement of a particular technology when alternatives are already reimbursed within a therapeutic class can limit physician/patient choice and the value of competing medicines. The more therapeutic options reimbursed within a therapeutic class, the more access to innovation. In Germany, the inclusion of medicines into SHI formulary is linked to EMA approval, so options within each therapeutic class is not limited by HTA decision. Apart from Germany, which reimburses all 6 targeted therapies included in our analysis, England and France also rank highly reimbursing 5 and 4 out of the 6 therapies, respectively. In England, where a targeted therapy does not receive NICE recommendation for reimbursement, there is provision for public funding through alternative public bodies such as Cancer Drug Fund to ensure full and timely public reimbursement of EMA-approved precision therapeutics.³²³

7. Budget to implement decisions: There is a correlation of TTM with country income levels and ability to pay, although there are other factors at play.³²⁴ Higher-income countries like England, France and Germany generally have shorter TTM for health technologies and the same trend is seen in access to innovative technologies like targeted therapies. This is perhaps due to higher spending (more budget availability) on biopharmaceuticals and innovation. France and Germany had higher pharmaceutical

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- 318 Ferrario, A (2018). Time to Entry for New Cancer Medicines: From European Union–Wide Marketing Authorization to Patient Access in Belgium, Estonia, Scotland, and Sweden. *Health Policy Analysis. Value in Health* 21(7): 809–821
- 319 EFPIA (2018). MEAs and innovative pricing models: Real world experience. Final Report
- 320 Prieto-Pinto, L., Garzón-Orjuela, N., Lasalvia, P., Castañeda-Cardona, C., & Rosselli, D. (2020). International Experience in Therapeutic Value and Value-Based Pricing: A Rapid Review of the Literature. *Value in Health Regional Issues*, 23, 37–48. <https://doi.org/10.1016/j.vhri.2019.11.008>
- 321 OECD (2020). Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward. OECD Health Working Paper No. 115, available at: <https://doi.org/10.1787/6e5e4c0f-en>
- 322 EFPIA Patients W.A.I.T. Indicator 2021 (IQVIA ATC4 class - J5C9, HIV antiretrovirals)
- 323 Cancer Drug Fund. National Health Service. Availability at: <https://www.england.nhs.uk/cancer/cdf/>
- 324 Costa-Font, Joan, McGuire, Alistair and Varol, Nebibe (2015) Regulation effects on the adoption of new medicines. *Empirical Economics* 49(3): 1101–1121. ISSN 0377-7332

spending than the EU average in 2020.³²⁵ Countries with lower budget capacity usually have longer TTM. For example, in Poland, new patient enrolment in a medicine access programme was delayed because of budget constraints.³²⁶ The availability of a dedicated budget for precision diagnosis as part of hospital budgets enables the adoption of biomarker testing in Denmark. The NHS has dedicated test funding at the national level to drive uniformity in access and encourages the uptake of NGS biomarker testing in England.³²⁷

8. Diagnostics and supporting infrastructure: The use of targeted therapies is largely dependent on the availability of infrastructure to support diagnosis, including predictive biomarker testing. Countries such as Denmark, England, France and Germany with high uptake of single and multi-biomarker test (such as next-generation sequencing) usually have higher patient access to targeted therapies.³²⁸ Laboratory access can be enabled either through high laboratory density or regional availability with efficient referral systems. A high density of laboratory facilities within a country provides access to biomarker testing. In Denmark and England, all biomarker testing including single and multi-panel biomarkers is centralised to regional or national hubs that perform all testing. In France, molecular diagnostic testing is centralised to the reference lab network. This ensures hospitals with no in-house capabilities have access to testing via established referral pathways.

In France, approval of biomarker tests is prompted by therapy introduction, and in Germany, immediately following the launch of linked therapies, immediately after EMA approval, ensuring prompt access. Availability of multi-biomarker tests such as NGS is usually higher in countries with centralised systems as economies of scale justify infrastructure investment. In England and Germany, multi-biomarker testing is centralised to regional centres, facilitating broad adoption of NGS capabilities nationally. In England, government policy on Genomic innovation (such as the 100,000 Genomes Project) has enabled the national-scale development and implementation of NGS facilities.³²⁹

9. Multiple layers of decision-making process: In some countries, there are multiple layers of reimbursement decision-making processes, from a national level to a regional level and then to the hospital level in some instances. In Spain, for example, regional

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- 325 OECD (2020). Health at a Glance: Europe 2020 : State of Health in the EU Cycle. Available at: <https://www.oecd-ilibrary.org/sites/78878924-en/index.html?itemId=/content/component/78878924-en#:~:text=In%20total%2C%20the%20EU%20retail,picture%20of%20overall%20pharmaceutical%20expenditure>
- 326 Vintura (2020). Improving time to patient access to innovative oncology therapies in Europe. EFPIA. Available at: <https://www.vintura.com/news/white-paper-every-day-counts/>
- 327 Normanno, N., Apostolidis, K., Wolf, A., Dieri, R. A., Deans, Z., Fairley, J., Maas, J., Martinez, A., Moch, H., Nielsen, S., Pilz, T., Rouleau, E., Patton, S., & Williams, V. (2022). Access and quality of biomarker testing for precision oncology in Europe. *European Journal of Cancer*, 176, 70–77. <https://doi.org/10.1016/j.ejca.2022.09.005>
- 328 Normanno, N., Apostolidis, K., Wolf, A., Dieri, R. A., Deans, Z., Fairley, J., Maas, J., Martinez, A., Moch, H., Nielsen, S., Pilz, T., Rouleau, E., Patton, S., & Williams, V. (2022). Access and quality of biomarker testing for precision oncology in Europe. *European Journal of Cancer*, 176, 70–77. <https://doi.org/10.1016/j.ejca.2022.09.005>
- 329 100,000 Genomes Project, available at: <https://www.genomicsengland.co.uk/initiatives/100000-genomes-project>

governments and local hospitals are responsible for the management of 90% of public health expenditure although decisions on public reimbursement and price setting remain centralised at the national level. While regional governments are not legally allowed to deny access to medicines with centrally approved public reimbursement, they are in charge of purchasing, managing, and paying healthcare providers and as such have a role in determining access to medicines. This type of decision-making arrangement prolongs the time to access for patients. Generally, countries in which lengthy negotiations with national and regional decision-makers have to take place, like Spain, have a longer time to patient access.³³⁰

10. Speed of uptake at provider level: In addition to drivers of faster TTM described above, there are demand-driven factors that can directly enable patient access and faster uptake of precision diagnostics and therapeutics. These include healthcare provider factors such as availability of full complement of well-trained oncologists, geneticists and pathologists; provider education (knowledge and awareness) on new innovations; inclusion and regular update of clinical guidelines and formularies with new therapeutic innovations; clear referral pathways for use of diagnostics to minimise patient leakage; and patient awareness of benefits of precision diagnostics and therapeutics to inform patient choice and compliance. In Denmark, England, France and Germany, referral pathways linking treatment centres to diagnostic facilities are well-defined with centralisation of biomarker testing and linkage with treatment centres. In these countries, there is also dedicated efforts to create awareness on benefits and availability of precision diagnostics and therapeutics through regular and well-publicised guideline updates and a focus on education of the clinical community.³³¹

330 Uyl-de Groot, C. A., Heine, R., Krol, M., & Verweij, J. (2020). Unequal Access to Newly Registered Cancer Drugs Leads to Potential Loss of Life-Years in Europe. *Cancers*, 12(8), 2313. <https://doi.org/10.3390/cancers12082313>

331 Normanno, N., Apostolidis, K., Wolf, A., Dieri, R. A., Deans, Z., Fairley, J., Maas, J., Martinez, A., Moch, H., Nielsen, S., Pilz, T., Rouleau, E., Patton, S., & Williams, V. (2022). Access and quality of biomarker testing for precision oncology in Europe. *European Journal of Cancer*, 176, 70–77. <https://doi.org/10.1016/j.ejca.2022.09.005>