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Personalized Medicine: Potential, Barriers and Contemporary Issues

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Resumo

A medicina personalizada (PM), é um modelo de prática médica personalizada a cada doente por meio da identificação de características individuais, como a sua informação genética, histórico familiar e estilo de vida, e ganhou relevância significativa nas últimas décadas à medida que os avanços tecnológicos permitiram a compreensão das diferenças biológicas entre indivíduos.

Além disso, a necessidade de uma abordagem mais econômica é considerada vital pelas várias entidades envolvidas nos cuidados de saúde. Na verdade, existem muitos potenciais benefícios da PM, incluindo a minimização do risco de toxicidade a determinados medicamentos e o aumento da eficácia dos mesmos, contribuindo assim para a sustentabilidade do sistema de saúde, e facilitando a descoberta de novas moléculas com ação terapêutica benéfica. Infelizmente, existem também muitas barreiras à sua implementação, nomeadamente aquelas relacionadas com custos, com a complexidade dos dados envolvidos, com a qualidade da evidências clínica, e a necessidade de educação e formação e de novas políticas regulatórias, barreiras estas que têm limitado a tradução clínica deste modelo médico para os cuidados de saúde atuais.

Nesta dissertação, pretendemos abordar as características que ajudam a moldar a PM, o seu impacto na prática clínica, e as barreiras que precisam de ser superadas para demonstrar o valor deste modelo clinico inovador. Esperamos ter abordado uma série de questões que destacam o potencial impacto benéfico da PM, tendo em consideração a heterogeneidade da doença e a variabilidade genética inter-individual, a importância da segurança nas análises preditivas e da identificação de biomarcadores de eficácia, a relevância da farmacogenómica, as mudanças necessárias no desenho dos ensaios clínico, fatores que no seu conjunto permitirão o desenvolvimento de uma abordagem clínica mais adaptativa. Embora o impacto da PM possa já ser confirmado através de vários exemplos descritos nesta monografia, há várias etapas a serem realizadas para construir um modelo médico mais robusto. Esses esforços são descritos neste trabalho, bem como o papel vital dos Farmacêuticos, É ainda apresentada uma abordagem esquemática para a implementação a PM na prática clínica atual. O investimento em investigação e educação, novas políticas regulatórias, a aposta em novas técnicas de análise de *big data*, infraestruturas tecnológicas inovadoras, e alterações de padrões da

indústria farmacêutica permitirão melhorar a qualidade de vida da população através da PM.

Palavras-chave: Medicina Personalizada; Farmacogenómica; Biomarcadores; Resultados Clínicos; Genómica Humana; Resposta à Medicação; *Big Data*.

Abstract

Personalized medicine (PM), which refers to providing tailored medical treatment to individual patients through the identification of common features, including their genetics, inheritance, and lifestyle, has gained significant relevance over the last decades as technological breakthroughs have allowed for the understanding of biological differences between individuals. Moreover, the need for a more cost-effective approach has also been deemed vital by the various stakeholders involved in health care. Indeed, there are many potential benefits of PM, including minimizing the risk of drug toxicity and increasing the efficacy of the drugs used, contributing to the sustainability of the healthcare system, and facilitating drug discovery and development programs. Unfortunately, there are also many barriers such as cost, complexity, high quality evidence requirements, the need for further education and regulatory policies, which have limited the clinical translation of this medical model to current healthcare.

In this dissertation we aimed to discuss on the characteristics that help shape PM, its perceived impact on clinical practice, and the barriers that have to be resolved in order to demonstrate the value of this innovative model. We hope that have addressed a number of issues that highlight the potential beneficial impact of PM, taking in consideration disease heterogeneity and genetic variability, the importance of predictive safety and efficacy biomarkers, the weight of Pharmacogenomics, and the importance of changes in the design of clinical trials that will enable a more adaptive clinical approach. Although the impact of PM is already in place to some degree, there are several steps to be made in order to build a more robust medical model. These efforts are described in this work, as well as the vital role of Pharmacists, and a schematic approach is proposed to implement PM into the current clinical practice. Research and Education investment, regulatory policies, big data analysis, technology infrastructures, and industry standards must be revised and change with the goal of securing patients' quality of life through PM.

Keywords: Personalized Medicine; Pharmacogenomics; Biomarkers; Clinical Outcomes, Human Genomics, Drug Response, Big Data.

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For the unique opportunity to be a part of this exciting project, I would like to express my deepest gratitude to my supervisor Professor Elsa Rodrigues. Thank you for your guidance and valuable feedback throughout the entire project

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Abbreviations

3-D - 3 Dimensional

BCL - B-cell lymphoma

BRAF - B-Raf Proto-Oncogene

BRCA1 - Breast Cancer Type 1 Susceptibility Protein

CCE - Cancer Core Europe

CDS - Clinical Decision Support

CNV - Copy Number Variation

CPIC - Clinical Pharmacogenetics Implementation Consortium

CYP1A2 - Cytochrome P450 Family 1 Subfamily A Member 2

CYP2B6 - Cytochrome P450 Family 2 Subfamily B Member 6

CYP2C19 - Cytochrome P450 Family 2 Subfamily C Member 19

CYP2C9 - Cytochrome P450 Family 2 Subfamily C Member 9

CYP2D6 - Cytochrome P450 Family 2 Subfamily F Member 6

CYP3A4 - Cytochrome P450 Family 3 Subfamily A Member 4

CYP3A5 - Cytochrome P450 Family 3 Subfamily A Member 5

DPYD - Dihydropyrimidine Dehydrogenase

EGFR - Epidermal Growth Factor Receptor

EMA - European Medicines Agency

ERBB2 - Erb-B2 Receptor Tyrosine Kinase 2

FDA - Food and Drug Administration

FHH - Family Health History

GWAS - Genome Wide Association Studies

HER2 - Human Epidermal growth factor Receptor 2

HER4 - Human Epidermal growth factor Receptor 4

HIV - Human Immunodeficiency Virus

HLAB - Major Histocompatibility Complex, class I, B

HRA - Health Risk Assessment

NGS - Next Generation Sequencing

PM - Personalized Medicine

PML/RARα - Promyelocytic Leukemia Protein Nuclear Body Scaffold / Retinoic Acid Receptor Alpha

RCT - Randomized Clinical Trial

SLCO1B1 - Solute Carrier Organic Anion Transporter Family Member 1B1

SmPCs - Summary of Product Characteristics

SNP - Single-Nucleotide Polymorphism

TPMT - Thiopurine S-Methyltransferase

UGT1A1 - UDP Glucuronosyltransferase Family 1 Member A1

VKOR1 - Vitamin K Epoxide Reductase Complex Subunit 1

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1 Introduction

1.1 Personalized Medicine

The underlying heterogeneity of many pathologies suggests that strategies for treating an individual with a specific disease, and possibly monitoring or preventing that disease, should be tailored or 'personalized' to that individual, in order to achieve a more effective and safer pharmacotherapy, instead of the current "one-size fits-all" approach (1).

Personalized Medicine (PM) utilizes the genetic, epigenetic, environmental, and clinical history of an individual, in order to improve the practice of medicine. Indeed, based on those characteristics, which are often associated with, and potentially causative of important changes in drug efficacy and adverse effects (2), we are now providing better disease prevention, more precise diagnoses, safer drug prescriptions and more effective therapies for the many diseases.

A multi-level approach towards patient stratification is essential for an accurate application of PM, and there are many variables that help distinguish patients with the same disease. Demographic and environmental characteristics, such as age, sex, ethnicity, and lifestyle, which are related to the risk of developing certain diseases and to the expected disease course and treatment response (3); Family history and inherited components of diseases allow a more focused prediction of an individual's health risks, facilitating greater patient involvement in generating their own personal data, and using it to guide their own medical management (4). Individuals' unique molecular profiles that determine differences in drug elimination pathways and resultant serum concentrations, as well as in drug targets and in the immune system, that can help predict the susceptibility to an expected drug reaction or to the a lack of response (5).

The key idea is to base medical decisions on individual patient characteristics rather than on averages over a whole population and to better Predict, Prevent, Treat and Cure.

1.2 Development of the Personalized Medicine Concept

1.2.1 The origin of Personalized Medicine

Although PM is an emerging field the rationality behind its development is not new. The recognition of differences in each patient's biology, genetic inheritance and

susceptibility to a disease are concepts that date the past centuries. Indeed, Archibald Garrod in his milestone book, "The Inborn Factors in Disease" (1931) (6), was the first person to recognize individual variation (or "chemical individuality") in both health and disease, and made the first connection between genetic inheritance and disease susceptibility, being considered the intellectual father of PM. These principles were translated into what today we propose as "the right drug for the right patient in the right dose at the right time". Nevertheless, only at the dawn of the 21st century has its impact on the patients and treatments been demonstrated, through the application of emerging technologies such as DNA sequencing, proteomics, imaging protocols, and wireless health monitoring devices, that have revealed great inter-individual variation in disease processes (7).

Interestingly, the term PM was only first introduced on 1999 by reporters Robert Langreth and Michael Waldholz, in a Wall Street Journal article that described the formation of the Single Nucleotide Polymorphisms (SNP) Consortium, a consortium established between a number of major pharmaceutical companies and academic research institutions (public and private collaboration), with the goal to provide a public resource on SNPs in the human genome. Its primary motivation was the possibility of developing drugs designed to target the individual patients' molecular and genetic makeups, and thereby individualize pharmacotherapy (6). A few months after publication of the article, it was reprinted in The Oncologist (6).

In 2003, the Human Genome Project, which consisted in the complete sequencing of the human genome, facilitated whole genome interrogation (8). It was possible to observe the extent of genetic variation in the human genome, but this massive variation was an enormous challenge for the characterization of alleles and haplotypes, that could contribute for the development of diseases in substantive ways. In other words, the challenge was to identify the few trait-altering variants that lie in an ocean of irrelevant ones (9). A breakthrough in this challenge was the development Next Generation Sequencing (NGS) and Genome-Wide Association Studies (GWAS) that provided the framework to associate specific genetic variants and their cognate genomic regions with diseases, even if the study design was not well suited to identifying the actual genetically causal variants. The approach was successful in that it provided much needed information to identify disease susceptibility genes and development biomarkers for diagnosis and therapeutic categorization (9, 10).

Genetic sequencing and genomics have come a long way since 2003. To uncover relationships that are not readily apparent between molecular profiles and disease states requires the development of novel data pipelines and computational tools. The combined analysis of multi-dimensional data is referred to as ‘panomics’. Panomics data, which includes not only DNA sequence from individual patients, but transcriptome, proteome, metabolome, microbiome and epigenome data, as well, has helped to identify phenotypes and to develop more efficient treatment strategies, evolving PM, beyond the genome, into the entire spectrum of molecular medicine (10).

1.2.2 Different words same goal

As stated before, PM is a relatively new medical and therapeutic approach for classifying, understanding, treating and preventing disease, based on information on individual biological and environmental differences (11). Over the past 20 years, different terms have been used to describe the individualization of therapy. During our research, we became aware of four main terms used to describe this new concept, namely Personalized, Precision, P4, or Stratified Medicine (12).

All these terms stretch from prevention to therapy, and refer to predictive, preventive, personalized and precision approaches in the medical context. There is no universally accepted definition, and most times these terms are used interchangeable to some degree, nevertheless, the concept of PM encloses the other concepts (Figure 1.1.). Actually, P4 Medicine stands for the clinical application of the tools and strategies of biological systems and medicine, to quantify wellness and demystify disease for the wellbeing of an individual (12); Stratified Medicine refers to matching therapies with specific patient population characteristics using clinical biomarkers (1); while Precision Medicine implies the integration of molecular research with clinical data from individual patients, to develop a more accurate molecular taxonomy of diseases, that enhances diagnosis and treatment, and tailors disease management to the individual characteristics of each patient (13).

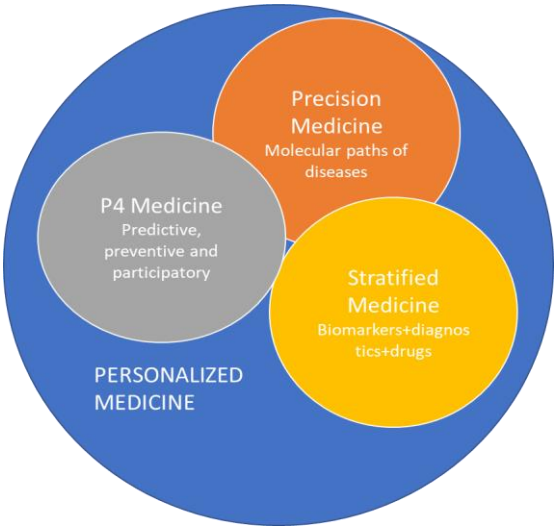

Figure 1.1. - Representation of the relationship/levels between the various terms that are used to describe Personalized Medicine. Precision Medicine, Stratified Medicine and P4 Medicine contribute with different clinical applications and belong in the universe of Personalized Medicine. Adapted from PHG Foundation (14).

1.3 Fundamental Components of Personalized Medicine

As mentioned in the upcoming chapters, we have many examples of Precision and Stratified Medicine in clinical practice. We are already capable of personalizing a therapy, with a pharmacogenomics approach that requires data collection followed by an appropriated analysis with the end goal of achieving the best treatment option available. Nevertheless, to enable the application of PM as a medical model there are other fundamental aspects that need to be addressed. Disease susceptibility and risk can be quantified and anticipated and shift the current paradigm of just disease treatment, to disease prevention as well (8).

1.3.1 Family Health History

Family health history (FHH) is a key predictor of health risk and has been a steadfast pillar of clinical practice. FHH is also referred to as medical history or case history. The specific type of information and depth of information collected may vary depending on the clinical setting and relevance to care. To be comprehensive, a complete FHH should include health information, social/ lifestyle history, medication history, ethnicity, ancestry and religion of a patient's blood-related first (parents, siblings, children), and second-degree relatives (half-siblings, aunts, uncles, grandparents), over three generations. To be optimally useable for analysis, FHH should

appoint both affected and unaffected family members, the age of disease onset, disease severity, any recurrences, and cause of death (15).

The introduction of personal genetic tests methods that identify carriers who might be vulnerable to a variety of medical conditions and diseases has raised the importance of first collecting and utilizing FHH to guide patient management in PM. Unlike personal genetic tests, FHH reflects shared genetic make-up, shared environment, or a combination, as such it is able to represent clinical information about disease mechanisms that are not well-captured by a genomic test-first strategy, such as rare variants and gene-gene or gene–environment interactions (4, 15).

There are pathologies where FHH is a well-established risk factor and is a more robust data source than the presence of predisposing genetic variants, like in type 2 diabetes, cardiovascular diseases, or some types of cancer such as colorectal cancers (CRC) (1, 7, 16). In the presence of a high-risk family history and a negative genomic test, patients are still at increased disease risk and warrant careful screening/monitoring.

In sum, FHH can provide information on disease risk, penetrance of a pathogenic mutation, classification of variants as pathogenic or not, and help identify novel disease-causing mutations, even more when combined with biomarker data analysis (17).

1.3.2 Health Risk Assessment

The second component are Health Risk Assessment (HRA) tools that calculate the probability of developing an event or a disease based on a prediction model or tools that make projections about the course of disease, measured by continuous outcomes (17). Enabling PM is not just a matter of availability of Big Data, generated from the genetic testing, FHH and clinical information of the patient, it also requires standard HRA tools capable of evaluating an individual's likelihood of developing a certain disease, in order to suggest different prevention strategies/ treatment regimens for patients who are at different levels of risk (15, 18).

One well-known HRA tool is the Diabetes Risk Calculator, which is used to calculate the probability that an individual has to develop either diabetes or prediabetes. The calculator includes questions on age, waist circumference, gestational diabetes, height, race/ethnicity, hypertension, family history, exercise habits and specific genomic biomarkers (7, 19).

1.3.3 Pharmacogenomics

The third element is Pharmacogenomics, which deals with the study of the genetic basis for varying response to drugs among individuals. Therapeutic decisions based on an individual's genetic profile critically impacts and enables the use of PM (20).

As mentioned before, by using high throughput technologies, we are now able to perform an exhaustive number of measurements over a short period of time giving access to not only to individuals' DNA variants (genomics), but to patterns of gene expression (transcriptomics), DNA methylation/ histone modifications and protein profiles of specific tissues and cells (epigenomics and proteomics), and metabolites (metabolomics), as well (21, 22). Pharmacogenomics used all this "omics" information to individualize drug selection and drug use, to avoid adverse drug reactions and to maximize drug efficacy (Figure 1.2.). The science underlying pharmacogenomics has advanced rapidly over the 50 years since it was first suggested that genetics might influence drug response phenotypes (23). There are now many validated examples of its clinical utility, stretching from variants that affect pharmacokinetics or pharmacodynamics, to tumour biomarkers used in cancer therapeutics (24).

Indeed, pharmacogenomics has its origins in the recognition that genetic variations in drug metabolizing enzymes and transporters influence the efficacy and toxicity of numerous drugs (25). Genetic polymorphisms in drug transporters and Phase I and II drug-metabolizing enzymes can alter the pharmacokinetic and pharmacokinetic properties of the administered drugs, their metabolites or both at the target site, resulting in variability in drug responses (26). Mutations in the genes coding region can lead to alterations in gene expression or protein structure, affecting protein levels and quality. In the case of enzymes, such mutations affect both the protein function and the rate and kinetic constants. Changes in drug-receptor or drug–enzyme interactions due to structural alterations of enzymes or receptors could also result in variations in drug responses (25, 26).

For instance, individuals carrying different in Cytochrome P450 Family 2 Subfamily C Member 6 (CYP2D6) allelic variants have been classified as poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), and ultrarapid metabolizers (UMs) according to the metabolic nature of the drugs and degree of involvement in drug metabolism of these variants (27). Another classic example is

related to the metabolism of Clopidogrel, a prodrug that is activated in the body primarily through CYP2C19. Like many other *CYP450* superfamily members, the *CYP2C19* gene is highly polymorphic, with >25 known variant alleles. The reference *CYP2C19*1* allele is associated with functional CYP2C19-mediated metabolism. The most common *CYP2C19* loss-of-function allele is **2* (c.681G>A; rs4244285), with allele frequencies of ~15% in Caucasians and Africans, and 29–35% in Asians (28). Other *CYP2C19* variant alleles in the coding region of the gene, with reduced or absent enzymatic activity have been identified (e.g., **3*–**8*), however, with low frequencies. Interestingly, the common *CYP2C19*17* allele (c.-806C>T; rs12248560), in the regulatory region of the *CYP2C19 locus*, results in increased activity as a consequence of enhanced transcription, with average multiethnic allele frequencies of ~3–21% (29). As far as clopidogrel metabolism is concerned, patients with reduced CYP2C19 activity are at risk for reduced activation and thus reduced antiplatelet effect. In 2010, the FDA added a boxed warning to the clopidogrel (Plavix) label to alert healthcare providers that some patients (roughly 2% to 14% of the population) do not metabolize the drug effectively and therefore might not receive its full benefits (30). Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines recommend against the use of clopidogrel in CYP2C19 poor metabolizers. Prasugrel or ticagrelor are alternatives that do not demonstrate this reduced therapeutic efficacy. These elements are then discusses with the patient and the physician, and it should be suggested that the surgery team considers the use of either antiplatelet alternative (30, 31).

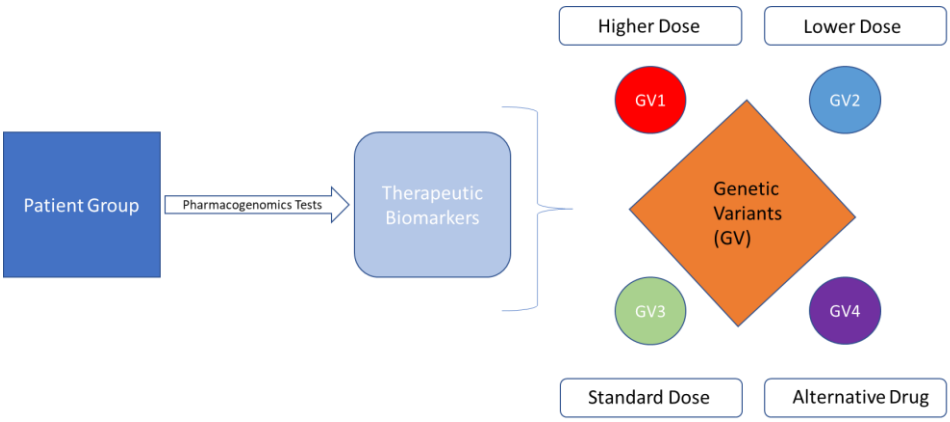

Figure 1.2. - Graphical resume of the effect that Pharmacogenomics has in clinical practice. From a Patient Group therapeutic biomarker are identified through

pharmacogenomics tests, which help to define and stratify the patients in accordance with major genetic variants. The expected drug response is predicted based on genetic background, which enables the application of the best therapeutic option available. Adapted from Zhang *et al.* (23).

1.3.4 Clinical Decision Support

The fourth and final component is the clinical decision support (CDS) system. CDS systems are interactive computer programs designed to assist clinicians in their decisions about disease care, and they are designed to link health observations with health knowledge to influence health choices by clinicians for improved healthcare (20, 32).

Currently existing digitized data and information are present in multiple formats and are largely unstructured resulting in silos of unused information. A critical step in PM is to integrate old and new data into validated information and to convert this information into knowledge directly applicable to diagnosis, prognosis, or treatment (33). By developing an integrated knowledge infrastructure that continually captures information, grows, accumulates, organizes, and institutionalizes new information, it is possible to access knowledge accumulated from scientific research and clinical data contained in medical records and apply it in a personalized medical decisions (27).

As formerly highlighted, PM is multi-dimension approach deeply connected to and dependent on data science. Artificial Intelligence (AI) leverages deep learning approaches to overcome the obstacles inherent in large data sets and unstructured data, inferring and describing causal links between different subcomponents (32). The FHH, HRA, pharmacogenomics and other data can be inputted on the system, which then provides disease risk prediction, diagnostic imaging prediction, or prediction of how a patient is likely to respond to the various therapeutic options available, and suggests the right drug for that particular patient (Figure 1.3.). Not only that, but this holistic decision-making process can help in determining the effective dose that fits the individual characteristics of a patient, his stage of life and genetic constitution (34).

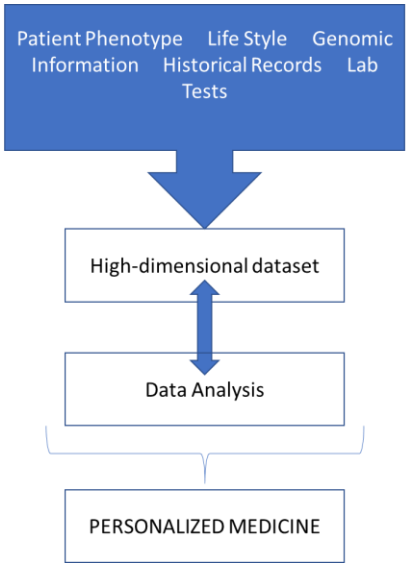

Figure 1.3. - Schematic representation of the decision-making process in personalized medicine. The genetic, epigenetic, family health history, environmental and social information's build a high-dimensional dataset which trough the proper data analysis method, personalized medicine is reached. Adapted from Zhang et al. (23).

2 Aims

Pharmacotherapy based on individual patient characteristics, such as their genetic makeup offer opportunities towards more effective treatment of disease, but also face numerous challenges. The aim of this project is to provide an overview of the current state of practice in PM, to describe future perspectives and to determine the opportunities and challenges that lie ahead.

For the sake of scoping, the focus of this paper is to describe the various components that shape this innovative medical model, understand the potential impact it can have on current healthcare, describe the major barriers that hold back its clinical application and determine the possible steps needed to bring this innovative approach to current clinical practice.

3 Materials and Methods

In order to write this monograph my approach consisted of a pragmatic review of literature focused on the impact and challenges of PM on the various healthcare systems worldwide, in order to determine the current state of its clinical practice and expected emerge.

To begin by consulting search platforms that comprise scientific literature from various areas, including PubMed (https://pubmed.ncbi.nlm.nih.gov/) , Google Scholar (https://scholar.google.com/) and ScienceDirect (https://www.sciencedirect.com/). This pragmatic approach was taken because of the large size and wide scope of PM literature. The search strategy was not intended to be exhaustive and instead aimed to retrieve those studies most likely to be relevant to the research question, while maintaining manageable numbers of records. The strategic English keywords used were manly: Personalized Medicine, Clinical Implications, Barriers, Challenges and Pharmacogenomics.

Besides review and search articles, fonts such as the sites of National Cancer Institute at the U.S.National Institute of Health (www.cancer.gov), the Pharmacogenomics Knowledge Base hosted by Stanford University, U.S. (www.pharmgkb.org) and The European Alliance for Personalised Medicine (www.euapm.eu) were used in order to supplement the literature review and provide insights and statistics on the measures made to date that shape the current state of PM and the current efforts being made as well.

4 Potential Impacts and Contemporary Issues of Personalized Medicine

4.1 Impact

Nowadays, the PM impact is increasing in numerous fields of applications, thus revolutionizing the medical practice. As previously mentioned, the advantages of PM include better medication effectiveness, since treatments are tailored to patient characteristics; reduction of adverse event risks through avoidance of therapies showing no clear positive effect on the disease, while at the same time exhibiting negative side effects; lower healthcare costs as a consequence of optimized and effective use of therapies; early disease diagnosis and prevention by using molecular and non-molecular biomarkers; and improved design of clinical trials due to selection of more likely responders at baseline. But to understand its real impact in clinical practice, firstly it is necessary to dissect the main areas of interest, focusing the attention on the actual findings and usage for each of them (23).

4.1.1 Drug Response and Biomarkers

Biomarkers are broadly defined as "A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention." (35). This comprehensive definition comprises therapeutic interventions and can be derived from molecular, histologic, radiographic, or physiologic characteristics. The analysis of human DNA, RNA and proteins, has led to the identification of mutations, gene variants, genetic anomalies and metabolic biomarkers that are associated with diseases onset and prognosis, and that can influence the therapy response (36). These molecular biomarkers can be *diagnostic biomarkers*, used to detect or confirms the presence of a disease or condition of interest, or identifies an individual with a subtype of the disease. Diagnostic biomarkers have evolved from the identification of patients with a disease, to the molecular and imaging-based classification of cancer. When a biomarker can be measured successively to determine the status of a disease for evidence of exposure to a medical product or environmental agent, or to detect an effect of a medical product or biological agent, it is considered a *monitoring biomarker*. One can also use *pharmacodynamic/ response biomarkers* level changes in response to exposure to a medical product or an environmental agent, which

is extraordinarily useful both in clinical practice and early therapeutic development. *Predictive biomarkers* can predict if an individual or group of individuals more likely to experience a favourable or unfavourable effect from the exposure to a medical product or environmental agent, while *prognostic biomarker* are used to identify the likelihood of a clinical event, disease recurrence, or disease progression in patients with a disease or medical condition of interest. Finally, *safety biomarker* can be measured before or after an exposure to a medical intervention or environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse event. In the future, complex composite biomarkers and digital biomarkers derived from sensors and mobile technologies, together with biomarker-driven predictive toxicology and systems pharmacology, will reshape PM (35). In summary, with the identification of these different types of biomarkers, today we can interfere in all the phases of disease: susceptibility and risk factors, preclinical progression, diagnosis, disease progression and therapy (9).

The use of molecular biomarkers has evolved from a single-gene assay to panels of dozens or more genes (37). Indeed, early testing was primarily composed of assays of a handful of variants in a single gene, targeted at the most common and most impactful variants. However new technologies, like NGS that may return the patient's entire DNA sequence for the required gene, or even the patient's genome, have allowed a large increase in the number of genes and variations viewed and the same time (31). As the result of the omics effort, more than 10 million SNPs have been identified, and extensive studies have been made to the identification of the subsets of variants relevant for determining haplotypes of clinical significance (38). PM recognizes that genetic profiling is now showing the potential to further tailor therapy and can be used in decision making, since the core aspects of this medical model is the use of genomic biomarkers (6, 39), together with nongenetic factors like age, sex to lifestyle to provide important phenotypic information which can be used for better therapeutic decision (22).

Indeed, molecular biomarkers are already used to identify patients who are likely to experience a favourable outcome of pharmacotherapy and thereby enable individualization and avoid inappropriate and often expensive treatments. For instance, variants rs8176085, rs799923, rs8176173, and rs8176258 in the Breast Cancer Type 1 Susceptibility Protein (BRCA1) gene are genetic variants associated with breast cancer

risk (40). In clinical molecular oncology many genetics variants identified in tumours are currently used to predict therapeutic response and genotype directed therapy has have a very positive effect on outcomes.

To better visualize the impact of these biomarkers, we will address four of the current commonly used predictive biomarkers in clinical molecular oncology testing and the impact they had on clinical practice. For instance, activating mutations in B-Raf Proto-Oncogene (BRAF) gene are present in approximately 40–60% of advanced melanomas. In 80–90% of cases, we can identify the BRAF V600E mutation, which is an activating mutation that consists of the substitution of glutamic acid for valine at amino acid 600 in exon 15. Vemurafenib is a specific inhibitor of activated BRAF and has been shown to significantly increase survival in patients whose tumour contains a V600E mutation in the BRAF gene, so the use of vemurafenib should be limited to patients whose tumour contains this mutation. BRAF testing and inhibition is also potentially relevant to other cancers in which BRAF mutations are common, such as papillary cancer of the thyroid (41-43). Another example is the hormone receptor status of breast cancer tumors, namely estrogen or progesterone receptor, can predict the outcome of hormone suppression therapy with tamoxifen or raloxifene. In hormone receptor-negative tumors, human epidermal growth factor 2 (HER2)/neu status will determine the efficacy of trastuzumab and lapatinib (42, 44). Among acute leukemia types, acute promyelocytic leukemia (APL) is rare and distinct subtype characterized by a chromosomal abnormality involving the t(15;17) (q22;q12) translocation, which results in fusion of the promyelocytic gene on chromosome 15 with the retinoic acid receptor gene on chromosome 17. Prompt diagnosis is essential because of the high frequency of life-threatening disseminated intravascular coagulation. All-*trans* retinoic acid has become a key component in therapy, as it induces differentiation of malignant promyelocytes to neutrophils, which can mitigate the coagulopathy seen in APL patients. With the introduction of all-*trans* retinoic acid, outcomes have drastically improved, with complete remission rates approaching 100% in all-*trans* retinoic acid-based regimens. In recent years with the addition of arsenic trioxide and anthracyclines, which have further improved outcomes, since abnormal promyelocytes are highly sensitive to anthracycline-based chemotherapy differentiate in response to all-trans-retinoic acid and arsenic trioxide treatment (42, 45).

In Table 4.1. we present a list of targeted therapies that have been approved to treat the most impactful types of cancer based on the currently most used biomarkers. So far, most advances regarding investments on research and development of drugs and corresponding biomarkers have been made in the field of oncology. This has likely been for a combination of reasons including the high cost per individual of pharmacological interventions, the potential for severe adverse effects with pharmacological interventions, the great unmet clinical need, the familiarity of oncologists with molecular pathology, and the relative ease of obtaining the required biological samples (36).

Predictive biomarkers can be developed in parallel to the drugs using the drug-diagnostic codevelopment model, which enables both the drug and diagnostic method market authorization. This means that molecular testing becomes an important part of the inclusion criteria when patients are enrolled in a clinical trial since a large part of the nonresponders can be screened out by the companion diagnostic test (32). The first treatment based on a monoclonal antibody guided by a diagnostic test was approved by the Food and Drug Administration (FDA) on 1998 for trastuzumab (Herceptin) and an immunohistochemical assay (HercepTest) for detecting HER2 overexpression in the tumor tissue was approved simultaneously with the drug (8, 36). The development of trastuzumab was the first drug to use the drug-diagnostic co-development model, in which a companion diagnostic assay is developed in parallel to the drug based on a thorough molecular understanding of the pathophysiology and the mechanism of action of the drug. Since the turn of the century this model has proven successful numerous times, especially within oncology and hematology (8).

Table 4.1. - Targeted therapies that have been approved to treat the most impactful types of cancer based on the currently most used biomarkers.

Drug	Tumor Type	Targeted Agent
Trastuzumab	Breast cancer and gastric cancer	HER2
Vemurafenib	Melanoma, colorectal cancer and thyroid cancer	BRAF
Imatinib	Chronic myleloid leukemia, GIST and myeloproliferative disorders	BCR
Ramucirumab	Gastric cancer, colorectal cancer and lung cancer	KDR
Vismodegib	Basal cell carcinoma	SMO
Atezolizumab	Bladder cancer	CD274
Bevacizumab	Brain cancer, cervical cancer and colorectal cancer	VEGF
Everolimus	Brain cancer, breast cancer, kidney cancer and pancreatic cancer	MTOR
Lapatinib	Breast cancer	HER1/HER2
Pertuzumab	Breast cancer	HER2
Palbociclib	Breast cancer	CDK4/CDK6
Cetuximab	Colorectal cancer, head and neck cancer	EGFR
Panitumumab	Colorectal cancer	EGFR
Nivolumab	Kidney cancer, lung cancer, lymphoma and melanoma	PDCD1
Rituximab	Leukemia and lymphoma	MS4A1
Dasatinib	Leukemia	BCR-ABL
Alemtuzumab	Leukemia	CD52
Gefitinib	Lung cancer	EGFR
Erlotinib	Lung cancer and pancreatic cancer	EGFR
Daratumumab	Multiple myeloma	CD38

A list of the top 15 drugs that have an approved companion diagnostic assay linked to their use in clinical practice are shown in Table 4.2.

With the recent approval of the immune checkpoint inhibitors targeting programmed cell death 1 or programmed cell death ligand 1, a new regulatory class of biomarker assays has emerged, which is the complementary diagnostic (46). This term is relatively new and was first introduced by the FDA when they approved nivolumab (Opdivo) for second-line treatment of nonsquamous non-small cell lung cancer. This term is used if during the review of the clinical documentation for a new drug and its companion diagnostic assay, it is determined that the assay is not essential for the safe and effective use of the corresponding therapeutic product, yet it identifies a biomarker-defined subset of patients that respond differentially to the drug and also aids the risk/benefit assessment for the individual patients simultaneously (6).

Table 4.2. - List of the top 15 drugs that have an approved companion diagnostic assay linked to their use in clinical practice.

Drug	Indication	Companion Diagnostic
Trastuzumab	Breast cancer	HercepTest
Afatinib	Non-small cell lung cancer	Therascreen EGFR RGQ PCR Kit
Alectinib	Non-small cell lung cancer	FoundationOne CDx (F1CDx)
Atezolizumab	Urothelial carcinoma	Ventana ALK (D5F3) CDx Assay
Binimetinib	Melanoma	Ventana PD-L1 (SP142) Assay
Brigatinib	Non-small cell lung cancer	THxID BRAF Kit
Ceritinib	Non-small cell lung cancer	Vysis ALK Break Apart FISH Probe Kit
Cetuximab	Colorectal cancer	Cobas KRAS Mutation Test
Crizotinib	Non-small cell lung cancer	Oncomine Dx Target Test
Cobimetinib	Melanoma	Cobas 4800 BRAF V600 Mutation Test
Dabrafenib	Melanoma	THxID BRAF Kit
Dacomitinib	Non-small cell lung cancer	Therascreen EGFR RGQ PCR Kit
Deferasirox	Thalassemia	Ferriscan
Enasidenib	Acute myeloid leukemia	Abbott RealTime IDH2
Encorafenib	Melanoma	THxID BRAF Kit

In Table 4.3. we present a list of drugs that are FDA has recently approved with a complementary diagnostic linked to their use. In contrast to the regulatory requirements for drugs that have a companion diagnostic assay linked to their use, testing with a complementary diagnostic is not mandatory before prescribing the drug, and testing information is not included in the labelling for the therapeutic product (46).

Identification of more stringent methods to screen patients' biomarkers could be a more pro-active approach to early identification and selection of patients in clinical trials. For example, liquid biopsies can detect DNA circulating in the blood. This type of biopsy is non-invasive, much lower risk than traditional biopsy and has been used to detect disease biomarkers extremely earlier (10).

Table 4.3. - Drugs that are FDA approved with a complementary diagnostic linked to their use.

Drug	Indication	Complementary diagnostic
Atezolizumab	Non-small cell lung cancer	Ventana PD-L1 (SP142) Assay
Durvalumab	Urothelial carcinoma	Ventana PD-L1 (SP263) Assay
Niraparib	Epithelial ovarian, fallopian tube, or primary peritoneal cancer	BRACAnalysis CDx
Nivolumab	Melanoma	Dako PD-L1 IHC 28-8 pharmDx

Another innovative approach is the use of Organoid Avatar Technology, *in vitro* structures resembling whole organs that are generated in 3-D culture systems. This avatars enable the generation of large "living biobanks," side-by-side with healthy tissue from the same individual with the potential to model developmental disease, degenerative conditions and genetic disorders, predicting and perfection the right approach without causing harm to the patient (47).

4.1.2 Clinical Trials Design

The emerging aspects of PM have also changed the way the development of a drug, and most predominantly, its clinical trial design is made. The traditional drug development track, where drugs are evaluated for safety in phase 1, early signs of efficacy in phase 2 and finally evaluated against standard therapy in a randomized phase 3 clinical trial has started to gradually fade out. With PM we are facing rapid phase 1 dose escalation trials, followed by strikingly large expansion cohorts and the emergence of new trials such as adaptive studies with basket and umbrella designs aimed at optimizing the biomarker–drug co-development process (48).

In umbrella trial design patient's eligibility is defined by the presence of a biomarker that is sub-stratified according to specific molecular alterations matched to different therapies (48). Several umbrella protocols, are already initiated to evaluate the role of PM in certain tumour types, such as the I-SPY1/2 in breast cancer (49), or the FOCUS-4 in colorectal cancer (50). The basket trial design includes patients with different tumour types with a common molecular alteration who are treated with the same matched therapy (48). The first basket study design ever made evaluated the efficacy of vemurafenib in multiple nonmelanoma solid tumours or haematological malignancies harbouring BRAF V600 mutations. With this design the activity of vemurafenib in BRAF V600E in lung, colorectal, and ovarian cancers was determined, as well as in people with rare diseases, such as Erdheim-Chester disease (51). This study is the first deliverable of PM that histology-independent, biomarker-selected basket studies are feasible and can serve as a tool for developing molecularly targeted cancer therapy.

A clinical study with an adaptive design is defined as one that includes planned opportunities to modify one or more specified elements of the study design and hypothesis based on data analysis subjects (52). Research into the accumulated data is carried out within the study at specific, prospectively planned time-points, and can be performed in a completely blind or a nonblind way. The final objective of adaptive designs is to learn from the accumulated data and apply what has been observed as soon as possible. The modifications to the study design that can be planned in the written protocol to cover a broad range of possibilities (53).

Well-known examples of adaptive measures in clinical trials include early stopping rules in case of lack of efficacy or unacceptable toxicity, and changing doses or schedules of drugs in order to improve the benefit/toxicity profile. More recently, novel adaptation strategies have been proposed. In the adaptive design, after the initial "learning phase", the ratio of patients randomly assigned to the experimental arm versus the control arm changes from the standard 1:1 to increase the proportion of patients randomized to the arm that is doing better, which augments the statistical power to detect a relevant magnitude of clinical benefit (52, 53). One can envision a trial that begins with a biomarker-stratified first stage until a pre-defined accrual is reached, and if the results of the interim analysis comparing the outcome of the experimental versus control treatment in biomarker negatives are not promising, recruitment in this arm is terminated and the second stage continues as an enrichment trial in biomarker positive patients until the planned total sample size is recruited (52).

Adaptive design trials have been shown to increase the efficiency of traditional clinical trials by facilitating the selection of the dose, reducing the number of patients exposed to ineffective or potentially toxic doses, aiding the precise calculation of sample size and reducing the duration and costs of clinical development (48, 54). For example, the Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) 2 study, is a biomarker-based and biopsy-mandatory prospective trial to guide treatment of heavily pre-treated metastatic Non-small-cell lung carcinoma patients (NCT01248247). In the "adaptive phase", randomization to different drugs or combinations is weighted based on mutation profile results generated in real time (55).

These new designs in early drug development enable the integration of preclinical data, the incorporation of information beyond the traditional dose-limiting toxicity period, findings from other trials and emerging safety data, thereby increasing the likelihood of accurately determining any benefit of a new treatment and complying more quickly with regulatory requirements for efficacy and safety (47). This model increases the weight of good predictors, and decrease the weight of unstable predictors, improving the overall performance of the classifier and selecting the 'best'-matched therapy to current patients' characteristics. These algorithms may facilitate the use of molecular signatures to predict the clinical outcomes of patients in prospective clinical studies (48, 56).

Both the European Medicines Agency (EMA) and the FDA have already recognized the validity of clinical trials with adaptive characteristics as a viable alternative strategy for both pivotal and early trials in the regulatory environment of pharmacological development (9). However, regulatory agencies are still reluctant in some cases to consider adaptive designs, as the results can be more difficult to interpret. One of the main concerns is the control of the type I error rate as well as the fact that adaptive measures may introduce bias (48).

A current example of efforts being made in Clinical Trials using this adaptive approach is the "The Basket of Baskets (BoB)" study, the spearhead Program of the Cancer Core Europe (CCE) (57). BoB is a modular, open label, phase II, study aiming to evaluate the antitumor activity of matched therapies in small CCE patient populations molecularly selected using a adaptive study design in an international multicentre basket design approach. The study consists of two parts (Figure 4.1.): Part A includes a molecular profiling program for subjects with advanced solid tumors (iPROFILER), that allows the molecular characterization of tumours from patients with metastatic or recurrent solid tumours and select the most suitable treatment for these patients; and Part B includes i-BASKET, is a multimodular basket trial, with different cohorts for genetically selected populations.

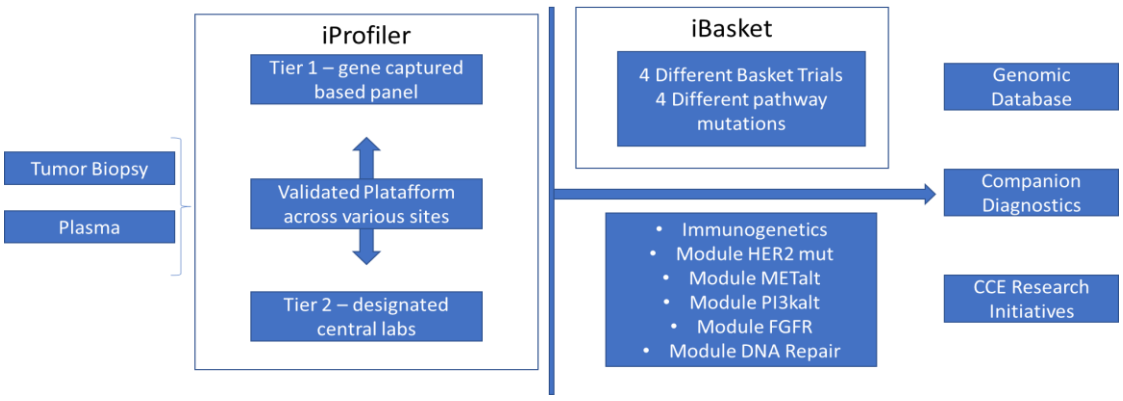

Figure 4.1. - Design of the Basket of Baskets platform sponsored by Cancer Core Europe. First, iProfiler selects subjects with advanced solid tumours and then a variant annotation tool and a molecular tumour board select the most appropriate treatment, validated across various scientific platforms. Afterwards, iBasket, a modular multi-arm basket trial for subjects with tumours harbouring selected molecular alterations, focuses on a certain molecular pathways or on certain molecular alterations (ex. Module HER2 (HER2 mutations); Module METalt (Proto-Oncogene Receptor Tyrosine Kinase (MET) mutations); Module PI3kalt (Phosphatidylinositol 3-kinases mutations);

Module FGFR (Fibroblast Growth Factor Receptor (FGFR) mutations), that may confer sensitivity to the study drug or study drug combination evaluated in that module/ arm. The final aim is to achieve drug repurposing of treatments, co-develop multi-marker companion diagnostics and a large database of knowledge in PM. Adapted from Garralda *et al.* (48).

The BoB study is testing therapies in multiple disease settings/ genetic contexts, encompassed by the development of companion diagnostics based on specific biomarkers in these genetic contexts, including circulating tumor DNA analysis as a way to select patients for any of the tested drugs and thus increase the efficacy of treatments. Its design allows both the development of sponsor-initiated trials and modular investigator-initiated trials, providing flexibility for adding new arms with different molecular alterations. This design also allows a more cost-effective use of the shared platforms and aims at dramatically accelerating new indications (repurposing) of the tested targeted therapies by providing clinical evidence of activity and validated companion diagnostics for use in confirmatory trials. This project will help bridge the existing gap between scientific discovery in basic and translational research and its application in a clinical research setting (48, 57).

4.2 Barriers and Contemporary Issues

PM has many potential advantages but as a disruptive innovation is also associated with a range of barriers. This has created the need for significant development in policy, education, clinical practice, and technology infrastructure. The current approaches to intellectual property rights, reimbursement policies, patient privacy, data biases and confidentiality as well as regulatory oversight will have to be redefined and restructured to accommodate the changes PM will bring to healthcare. The benefits surpass its many barriers and make the leap from hype to reality and be implemented in clinical practice (58-60).

4.2.1 Regulatory and Guidelines

To overcome the barriers to clinical application of Pharmacogenomics, several academic, medical, and community centers have initiated Pharmacogenomics implementation programs. The Pharmacogenomics Knowledge Base (PharmGKB) is a pharmacogenomics knowledge resource that encompasses clinical information including dosing guidelines and drug labels, potentially clinically actionable gene-drug associations and genotype-phenotype relationships. PharmGKB collects, curates and

disseminates knowledge about the impact of human genetic variation on drug responses (61). The CPIC and the Dutch Pharmacogenomics Working Group try to overcome the difficulty in translating genetic laboratory test results into actionable prescribing decisions for affected drugs. CPIC's goal is to address this barrier by creating, curating, and posting freely available, peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines. CPIC guidelines follow standardized formats, include systematic grading of evidence and clinical recommendations, use standardized terminology, are peer-reviewed, and are published in a leading journal with simultaneous posting to cpicpgx.org, where they are regularly updated (62).

To increase clinical utility, PM needs a CDS that synthesizes available data, including regulatory mandatory labelling language, medical centres coverage decisions, clinical practice guidelines, and systematic reviews, and offer interpretations regarding the strength of evidence for clinical implementation (63). There is still not an adequate standard regulatory guideline, that compiles all the information on how and when to use omics data, biomarkers, and appropriate weighting of relevant health outcomes for risk assessment, all important component of the decision-making process in PM (64).

There also exists a gap between evidence of association and the clinical utility of this data, and there is a need to overcome this challenge by exploring evidence from a health-care providers, patients, and policy perspectives. Associations between genetic variation and related outcome must be quantified for it to have a height in the decision process of the right treatment. Nevertheless, pharmacogenomics-related data and tests are already available for some drugs, so this knowledge has not been potentially translated into clinical practice at a bigger scale (22, 65, 66).

A good example of the direction to take is the "G-standaard", a Dutch drug database used by pharmacists, doctors, wholesalers, and health insurance companies. This database contains decision-making support information and is incorporated into electronic prescribing systems and pharmacy information systems (67, 68). The pharmacogenetics guidance consists of therapeutic recommendations for prescribers, assuming patients are genotyped pre-emptively. Both pharmacokinetic and pharmacodynamic gene-drug interactions have been included in the database. The drugs are associated with the following genes: *CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5*, Solute Carrier Organic Anion Transporter Family Member 1B1 (*SLCO1B1*), UDP Glucuronosyltransferase Family 1 Member A1

(*UGT1A1*), Thiopurine S-Methyltransferase (*TPMT*), Major Histocompatibility Complex, Class I (*HLA-B*), Vitamin K Epoxide Reductase Complex Subunit (*VKOR1*), Dihydropyrimidine Dehydrogenase (*DPYD*), and factor V Leiden (67). But the application of these guidelines has been limited up to now. One of the reasons for this is the limited number of patients that have been genotyped pre-emptively. If several countries adopt this system into their general practice more data can be generated and more concrete evidence will be generated (68).

Changing the clinical paradigm to pre-emptively sequencing patients at high risk of needing specific medications and provide parallel CDS around results interpretation and actions, could minimize the challenges, by cost-effectively interrogating a large panel of genes and integrating clinically actionable results into the patients clinical records, that can be used by clinicians at the point-of-care during the initiation of a treatment regimen (69). A distinct advantage to this approach is the ability to review the available sequence data, and based on new pharmacogenomic discoveries, update the patient's record without the need for additional specimen collection and testing provided that the variant was in a CDS and integrated in the patient clinical record (70). This increases awareness of drug-gene interactions, facilitate knowledge and acceptance of pharmacogenomic testing, and guide the individualization of drug/dose selection (69).

Another profound challenge is the harmonization of data and databases, patient privacy, cybersecurity, and data sharing. A project in which this is seemingly overcome is Genomics Evidence Neoplasia Information Exchange (GENIE), a transatlantic oncology data-sharing project (71). This project is an international pan-cancer registry of real-world data assembled through data sharing between 19 leading international cancer centres with the goal of improving clinical decision-making. After sequencing a patient's tumour, members on this program have three months to submit the data to Sage Bionetworks, a non-profit organization in Seattle, Washington. For the next 6 months, only the contributing institution can see that patient's record within a shared database. For the subsequent 6 months, it will be open to the full consortium. Finally, the patient's data becomes available to the broader research community (68, 72).

4.2.2 Big Data Analysis

Availability of biomedical data such as clinical imaging, Electronic Health Records, genomics and laboratory tests, patient history, sensors and wearable devices create increasing opportunities to obtain more precise and in-depth insights for patients. Nevertheless, this overwhelming information brings increasing challenges. The biomedical data mentioned above is usually large-scale, noisy, sparse, incomplete, irregular, heterogeneous, high-dimensional, generally unstructured and poorly annotated (23, 73). Deep learning is often proclaimed, as a powerful prediction tool that will revolutionise disease screening and diagnosis. This is well suited to examining complex high-dimensional data that would be challenging to model using conventional approaches. Such strategies have allowed the development of several innovative diagnostic algorithms: for example, to identify patients most in need of intervention from knee MRI (74), to detect cardiac arrhythmias from electrocardiograms (75), and to diagnose pneumonia from chest x-rays (76).

Another main difficulty is the management of the Big Data. This issue includes: data storage and processing, data integration and interpretation, generation of cost-effective of Big Data and individual and global cost relevance (77). Major investments also need to be made in bioinformatics, biomathematics, and biostatistics to accelerate the transition to PM, since they are critical to process all the data involved in this medical model, and then to differentiate all the different levels of casualty in order to reach the best outcome possibly (32).

In many cases, it is impossible to identify a single stratification factor or biomarker for patient populations. This is because many diseases (including cancer and various neurological and immunological diseases) are complex and affect a multitude of biological sub-systems. Accordingly, drugs for treating these diseases often target multiple proteins and associated biological processes. Identifying marker signatures is difficult and requires state-of-the-art approaches offered by data science (32, 78).

Enabling PM is not just a matter of availability of big data and sufficient computing power, it needs to be easily interpreted for a better prediction of outcomes and most important have a relevant validity to choose the best approach. So the dream of PM crafted by machine learning currently falls short of the expectations due to insufficient prediction power, difficult interpretation of results and insufficient validation.

Machine learning methods capture and mathematically describe a signal that is present in datasets. Their success does not only depend on the number of samples, but also on the signal-to-noise ratio. Separating true signal from technical noise is one of the key challenges in big data analysis. More generally, the prediction performance of any machine learning model is limited by the descriptive power of the employed data with respect to the clinical endpoint of interest. For example, non-common genomic variants that might be relevant to stratifying patients are not sufficiently represented in the data. On the other hand, genomic data is mostly static (at least in non-cancerous tissues) and misses potentially important longitudinal clinical information. For each prediction problem, it is therefore critical to identify and combine the right data modalities that could contain parts of the relevant signal when starting to build machine learning models. Shortcomings can result in loss of prediction performance. Many machine learning models developed for PM do not have a predictive power close to the high (and potentially unrealistic) expectations of clinicians (32, 56). Some of the reasons for poor prediction in PM are related to the fact that relationships of specific characteristics to clinically relevant endpoints are complex and non-linear, often varying over time and be partially influenced by factors that are not patient intrinsic like social and environmental influences. Furthermore, discriminating relevant from irrelevant patient-specific features is always a challenge in the field of biological high throughput data (32).

While machine learning techniques can detect complex patterns in large data and provide accurate predictions, they are unable to provide a deeper theoretical, mechanistic, or causal understanding of an observed phenomenon. Data science and AI thus do not replace classical, hypothesis-driven research. One reason is that machine learning models typically only capture statistical dependencies, such as correlation, from data. However, correlation does not imply causation. This is reflected by the fact that a multitude of biomarker signatures yielding similar prediction performance can be constructed to separate the same patient groups. Even if an acceptable prediction performance can be achieved, the lack of a clear causal or mechanistic interpretation of machine learning models can hinder acceptance of data science-based solutions by physicians (23, 32).

The maintenance of existing CDS architectures and the formation of new programs for delivering data will represent a significant opportunity in the coming years (34). Several

health systems have begun using CDS tools to integrate pharmacogenomic data into the clinical decision process and provide information to providers at the time when it is most valuable. Such CDS tools will be paramount as pharmacogenomics become more common and new formats for results and testing arise. Focus may also be applied to the development of patient-facing apps and portals through which the patient may interface with his or her providers and receive counselling on the results (31).

4.2.3 Ethical and Privacy issues

The high-dimensionality data created using genomics and other 'omics' technologies are central to many of the predictive, diagnostic and therapeutic applications of PM. However, the substantial increase in individual health information this approach requires, is also one of the main sources of ethical, legal, and social concerns regarding PM. Individuals may suffer from embarrassment, stigma, discrimination, and other harms to their dignity if sensitive information is inappropriately disclosed (79).

Because genetic data is unique, has a predictive rule, shows the risk of future diseases in individuals or their offspring's, and remains stable during life, genetic exceptionalism makes genetic data far different from others. In this regard, interfamilial privacy issues or the right of the family member to get informed about the risk of a disease which may influence his life should be balanced against patient's privacy (79, 80).

Ethical issues are also associated with the use and storage of genetic information of an individual (59), due to the large amount of information from PM that might be captured in biobanks, informed consent to use the patient data for research/ innovation is increasingly challenging. For that reason a layered and staged model of consent is currently being applied by the FDA. Some information becomes immediately available to everyone; more detailed information becomes available to those who seek to keep the core information comprehensible and manageable (65). Moreover, informed-consent information is not provided all at once, so patients are provided with more time to absorb the information step by step (68).

Making data available to different health care workers or researchers may increase the amount of information that becomes available to third parties, such as insurance companies or employers (81). This leads to the following concern that genetically at-risk individuals might be excluded from many goods, services, and activities.

Policymakers are therefore motivated to implement legislative solutions to overcome and prevent genetic discrimination (68, 82). In addition, insurers at both the national and international levels should adopt policies that explicitly state that they will not seek access to the results of genetic tests (68).

Ethical issues regarding accessibility and equality of different populations throughout different countries may also further increase the disparity between different health systems and the capacity of populations with lower incomes to access this novelties early on in the implementation life cycle of PM (83).

4.2.4 Financial Costs

Another set of challenges that threaten to exacerbate health disparities in the coming decade are economic barriers that both limit access to healthcare and reduce the benefit patients can derive from that care. This characteristic is common to many new healthcare technologies because if patients are unable to access a new technology, then they are also unable to enjoy the benefits of that technology (7).

There is a large disparity between the distribution of people and global health expenditures across geographical regions, and PM may further increase these disparities. In countries with private insurance systems patients with comprehensive health insurance coverage or the ability to cover such costs out-of-pocket will be able to undergo new tests and receive the benefits of individualized treatments despite their cost. Patients with no insurance, as well as patients with insurance designed to provide only urgent care, are unlikely to benefit from these advances (59, 84).

The laboratory tests that inform personalization are still quite expensive. When performed as a stand-alone diagnostic with a need for rapid turnaround, the cost-effectiveness of single-gene genotyping is difficult to obtain. Genotyping multiple genes in a single assay is more cost-effective and uses the DNA in the sample more efficiently (85). Finally, the most efficient analysis is to sequence the complete genome. The cost of sequencing a whole genome has dropped dramatically in the last years due to NGS. Currently, the costs less than $1,000 and that price is expected to fall even more when more commercial sequencing facilities are built (68, 86). Reimbursement is also an important issue: to date pharmacogenetic testing is only reimbursed, in the private sector, after an initial medication in cases in which the treatment turned out to cause severe side effects or was ineffective. Moreover, pre-emptive genetic testing

(screening) is not covered by National Health Systems and health insurances, partly due to the lack of robust evidence of the clinical-effectiveness and cost effectiveness of prognostic tests, so the risk of not adding value affects this decision (87). Indeed, the aspect of timing also needs to be thoroughly debated not only in terms of cost-effectiveness, but also in terms of the ethical issues it can raise. Is it better to sequence pre-emptively early in life, so that the results will be available for clinical use throughout a lifetime, or only should genotyping been done by request (68). For instance, the PG4KDS protocol aims to establish processes for using pharmacogenetic tests in the electronic health record to pre-emptively guide prescribing (88). St. Jude Children's Research Hospital pre-emptively genotypes patients for 230 genes using the Affymetrix Drug Metabolizing Enzymes and Transporters Plus array supplemented with a CYP2D6 copy number assay. As of June 2020, PG4KDS pharmacogenetic test results were being used in the health records for nearly 6,000 St. Jude patients.

Moreover, an additional source of increased costs will be the interventions that are recommended taken in consideration the laboratory test results. For example, pharmacogenomic testing may have the potential to decrease overall costs at the level of the healthcare system, but at the level of individual patients, however, many are still likely to end up taking medications with higher direct costs compared with the standard therapy (82).

Assuming the costs will drop, cost-effectiveness studies should be made and have to focus on how to interpret and deploy genetic variants to improve medication prescription (89). There have been some studies published but each generally examined narrow fields of PM, for example Verbelen and coworkers looked at pharmacogenetic guided treatment (90), Grosse and collaborators examined specific diseases or risk factors, while Plumpton and colleagues looked at adverse drug reactions (91).

5 Discussion

5.1 Future Perspectives

PM shows great promise but is yet to live up to its expectations. Although there is extensive preliminary evidence of the benefit of many markers for guiding pharmacotherapy, very little of this research has been translated into the clinic. There are several important barriers responsible for this situation, that once overcame will lead to a revolution in healthcare. Several steps have to be made in order to build an infrastructure capable of welcome PM into clinical practice (68). A diagram of a possible implementation strategy of PM is shown in Figure 5.1.

Step 1 – Promote Research in PM

Prioritize research-funding of PM based on potential clinical utility. Focus first on existing products and the development of suitable diagnostic techniques based on valid biomarkers enabling the efficient use of these existing therapy options. The focus should be on i) diseases for which the effectiveness of medicinal products is largely variable, leading to variability in expected results; ii) medicinal products with narrow therapeutical window and serious side effects; iii) products for which the time needed to evaluate the clinical effects is relatively long, while the nature of the disease is progressive; and product groups with high budget impact (89, 92).

The clinical relevance of testing is not always clear and valid data is largely missing. The existing research and development framework has to be less linear and became more adaptive. By intertwining research and clinical practice more extensively, data from clinical practice can be used for research more easily, and research knowledge can be used more quickly translated into clinical practice (8, 68).

In addition, there are currently no incentives to invest in clinical trials with products that are out of patent. PM research could help repurposed some products that could have an impact in important clinical problems like those in areas like oncology or neurology. Revitalizing the life cycle of this products could prove financially advantageous (93).

Step 2 – Regulatory System

Incorporate the amount and nature of PM clinical evidence data in the regulatory systems of marketing authorization, reimbursement, and health care economics so to ensure a regulatory environment capable of incorporating PM.

PM implies the prescription of a medicinal product to a subset of patients or even tailored to one single patient. The current standards for marketing authorization and cost-effective analysis, usually a randomized controlled trial, are not always possible, often due to the small number of patients. Therefore, other trial designs and other levels of evidence to prove clinical efficacy and safety are necessary. Examples of this are adaptive designs, models for prediction of response, the use of longitudinal data and the use of real-life data (48, 64), which have previously been addressed.

Regulatory Agencies should extent the existing Summary of Product Characteristics (SmPCs) of medicinal products with guidance on how to handle them in cases of specific genetic variants, if clinical validity and utility are supported by the adequate scientific evidence. This is especially important because the SmPCs are directly or indirectly used as an information source for formularies, prescription guidelines and databases used by health care professionals (64, 94).

Guidelines will play a crucial role in the uptake of PM in clinical practice. The inclusion of PM in guidelines should be supported, together with efficient ways to quickly update guidelines when new information becomes available. These guidelines should be prepared with health care professionals, health insurance companies, testing facilities and Regulatory Agencies worldwide, to facility standardization in genomics data generation and handling. These steps should provide guidance on the kind of data needed to assess clinical utility and cost effectiveness, and standardize at least clinical sampling, analytical testing, data analysis, data interpretation, data storage, data exchange and visualization of data for health care professionals and patients (68).

Step 3 – Data Infrastructure

Build a suitable framework for patient data generating and storage. The primary focus should be to create guidelines for storage, ownership, and possibilities to consult multiple databases, since, has previously mentioned, there are a lot of concerns regarding privacy and security of patients.

It is more than evident that PM generates a big volume of data, so in parallel, computational methods must advance in order to provide direct benefit to clinical practice. Current algorithms are far from being able to recommend the right treatment at the right time and dose for each patient. Steps that bring us closer to this goal could be investing in innovative software tools, that better link knowledge with machine learning-based predictions from multi-scale, multi-modal, and longitudinal data; innovative modeling approaches, such as causal inference techniques and hybrid modeling, which go beyond typical state-of-the-art machine learning; new computational modeling approaches that allow us to identify critical transitions in a patient's medical trajectory (56, 95).

While the current standard is to map the most relevant molecular features in a machine learning model onto biological pathways, this approach could be further enhanced to make machine learning-based decisions interpretable by clinicians, like having a software system that automatically collect information on each variable from various databases and publications that are previously validated and standardized via guidelines and regulation (32).

Step 4 – Education

Health care providers, including doctors, physicians, pharmacists, and nurses, need to be trained in how to generate omics data, interpret these data and to learn how to make clinical decisions based on it. Education is also needed to allow health care providers to discuss the pros and cons of genetic testing with patients. In parallel, bioinformatics and statisticians have to increase their knowledge in biomedical education in order to be able to interpret large datasets related to PM.

The formation of these multidisciplinary professionals has to start at a college level, where specific courses are available, and continue to be available as part of post-graduate development programs (21, 78).

Step 5 – Awareness

It is necessary to raise awareness and understanding amongst the general public regarding the possibilities and limitations of genetic testing and to empower patients to

make informed decisions. Awareness activities should focus on informing people about possible applications and the kind of testing options that may be offered to them, including the issues related to genetic testing like privacy, data ownership, incidental findings and risk evolved. Empowerment is necessary for shared decision-making in cases in which genetic testing will be offered as an opportunity in pharmaceutical care or other health care options, including prevention (13).

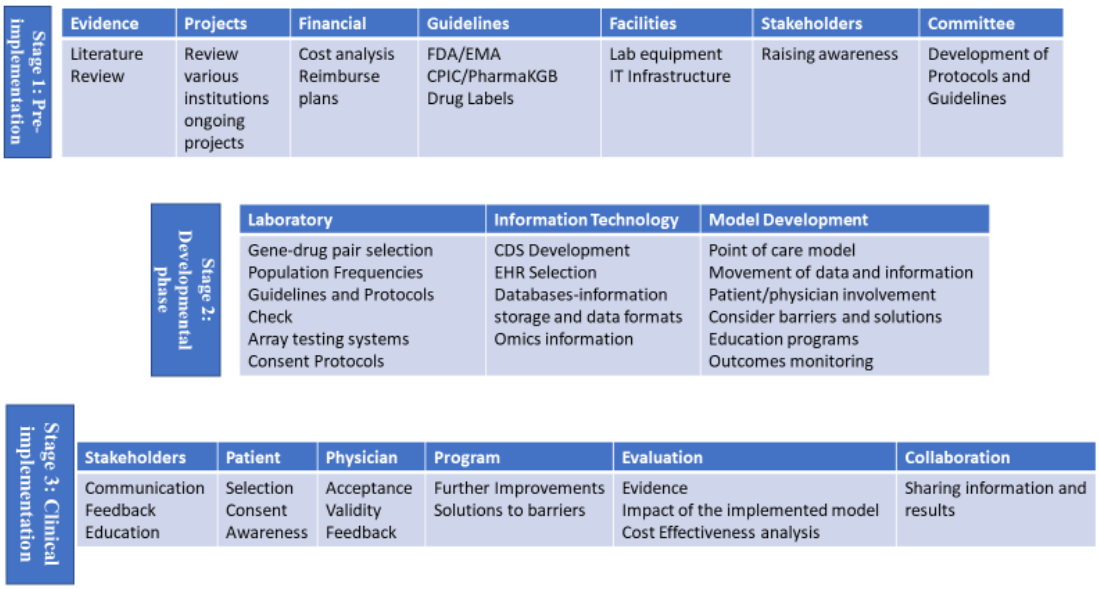

Figure 5.1. – Possible Implementation strategy of Personalized Medicine. Stage 1: Pre-implementation: research and synthesis of data are gathered to prepare for application. Stage 2: Developmental phase: all the information assembled is used to develop a suitable workflow model form laboratory to point of care, as well as an Information Technologies Infrastructure. Stage 3: Clinical implementation: through the use of the workflow model, where the former measures come to fruition and are used in clinic practice. The results are then recorded and can be used to improve on other possible solutions. Adapted from Klein et al. (59).

5.2 Role of the Pharmacist

The field of PM affords multiple opportunities to the pharmacist profession. Pharmacists are the only health care professionals who are specifically trained to understand and apply the fundamental sciences of pharmacokinetics, pharmacodynamics and clinical pharmacology to patient care, which makes them uniquely suited to use this medical model in clinical practice (96).

The profession of pharmacy has evolved from a dispensing model focused on the formulation and delivery of a drug product, to a patient care model focused on individualizing drug therapy and delivering direct patient care based on a given patient's age, size, organ function, concomitant treatments, diet, allergies and disease states (96, 97). Pharmacists are also currently providing services such as glucose testing, cholesterol screening, blood pressure monitoring and immunizations in community pharmacies and ambulatory clinics, increasing the personalization and monitoring of patient care (98).

As we can see, there is already an attempt of a personalized approach made by the pharmacist. However, to push this concept even further, the use of clinical pharmacogenetics has to be explored since it has the potential to redefine the professional identity and accelerate the implementation of PM (99).

When assessing the readiness of pharmacy for PM, one must consider factors that are specific to the profession as well as systematic considerations that allow pharmacists to successfully integrate PM into their individual practice area. These factors, which have been described in the previous chapters, include education, training, clinical validation of results, technology/laboratory infrastructure and financially sustainable practice models, but the most critical component of building confidence and ensuring competency in PM will be the availability of adequate support, mentoring and guidance for pharmacists to develop their skills in pharmacogenetics (96, 100).

The first step in a successful advancement of clinical pharmacogenetics requires clearly defining the profession's vision of what the end goal is by defining the skills that pharmacists need to understand in order to translate the genotype-related data into clinical practice, and deciding if this will be a core responsibility required of all pharmacists or if will it be a sub-specialty of pharmacy practice (99, 101). By building robust education bases, this in turn will build confidence and foster engagement providing the necessary momentum to move the discipline and profession forward (96). Creation of a single, unified vision for how pharmacogenetics will fit into the profession of pharmacy will also require involvement of key stakeholders such as system administrators, health policy makers, information technology specialists, insurance companies and laboratory medicine (102).

Pharmacists are also the most accessible health care providers in the community, and the ready availability of genetic testing kits in community pharmacies presents a tremendous opportunity for generating results, patient education and counselling. The community pharmacy is often the one place that links prescriptions from multiple prescribers and health care providers, given that patients tend to see many providers but only visit one pharmacy. The community pharmacy could, therefore, serve as a centralized "hub" for PM information. Expertise in pharmacy is also critically important in other areas required for implementation of clinical pharmacogenomics, such as pharmacy informatics, CDS tool development, database management, development of medication use policies and processes, logistics of genetic testing, research and clinical guideline development (96, 103).

An essential step for clinical pharmacogenomics implementation is understanding the different PM areas in which pharmacists can impact such as: in regulatory policies and processes, by planning the health system infrastructure and approval requirements; in literature evaluation of evidence-based medicine, because new data can quickly lead to updates in PM implementation; in informatics due to the significant role of electronic CDS; in research and ethical issues, since managing patient data is key to the creation of legislation in the clinical research field; and in direct patient care by assisting in the decision making and in directly implementing different personalized therapeutic approaches, depending on patient data and/or in the application of genetic tests (103).

Successful practice transformation requires opportunity, expertise and a spirit of engagement, and these elements are already in place with respect to the Pharmacists profile (96).

6 Conclusion

This report attempts to summarise what is the current state of PM and to identify the major contributions to date, as well as the biggest hurdles that have to be surpassed in order to bring this innovate model to clinical practice.

After the research made for this project, it is my firm belief that many of the hurdles in translating PM research to clinical practice that have been mentioned are interconnected, and that the opportunities are already being recognized and addressed. Nevertheless, the evolution has been done at a very slow pace, since many of the challenges that were firstly recognized several years ago, still remain.

I believe that the currently generated PM results do not fit in well with the current regulatory and assessment designs. This is especially the case with the assessment of clinical validity (trial designs) and clinical utility (choice of criteria, cost-effectiveness). Several key technologies for genetic testing, risk assessment and CDS have to be constructed specifically for PM, since it involves an amount of data different from any other, and an analytic power only possessed by machine learning models. Healthcare systems must also be organised in ways that support the adoption of such a model, as exemplified by the Genomics England project. PM strategies requires health care providers to be adequately trained, and most importantly, challenges posed by pricing and reimbursement must be resolved, if the pharmaceutical industry is to continue to lend its weight to the development of more targeted, effective and ultimately valuable products.

To date one of the best endeavours in enabling and building basis to clinical application of Personalized Medicine has to be the 100,000 Genomes Project which represented a step forward in making genomic medicine a reality for the National Health Service in the United Kingdom. Whole genome sequencing of 100,000 genomes from NHS patients with either cancer or a rare hereditary disease was accomplished and established a genomic medicine service for the health system, provided clinical diagnosis with new personalised treatment options, enabled scientific discovery and facilitated patient engagement with genomic medicine. This big step can serve has a guide to other countries with similar Health Care Systems and with the means to invest and to apply them.

In sum this revolution will only be possible to achieve by equal contribution of patient and consumers in participating in clinical trials; entrepreneurs and innovators to develop tools that analyse information; regulators by educating consumers and providers, and by supporting essential revolutions in policy and regulation; physicians to understand the disease at the molecular level; academic researchers by accompanying innovative research to uncover new insights at the molecular basis of disease and supporting target-based drug development; the information technology sector by creating unique electronic tools to collect and secure patient information; stakeholders, payer and policy makers by exploring new business models, novel diagnostics tools, target therapy and other personalized treatment protocols; and finally pharmacist with their expertize in from clinical pharmacology to patient care.

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