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# Ιατρική Ακριβείας στο Πλαίσιο του Ευρωπαϊκού Δικαίου: Ηθικές Παρατηρήσεις και Νομικές Προκλήσεις

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Πρωτότυπη Εργασία

# Navigating Precision Medicine Within European Law: Ethical Considerations and Legal Challenges

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## Abstract

Precision medicine, characterized by personalized treatment strategies based on extensive patient-specific data, has gained prominence in recent years. This paradigm shift from the traditional one-size-fits-all approach aims to optimize healthcare outcomes by integrating genomic, clinical, and lifestyle information. While precision medicine's transformative impact in fields like oncology and pharmacogenomics is evident, regulatory frameworks, including GDPR, Clinical trials regulation, IVD regulation, and the recently effective Health Technology Assessment Regulation (HTAR) from January 2025, are scrutinized for their contributions and identified gaps. Despite significant progress, challenges persist, including issues related to informed consent, companion diagnostics, direct-to-consumer genetic tests, intellectual property rights, and diverse healthcare policies across the EU. The lack of global harmonization adds complexity to regulatory environments. The conclusions stress the dynamic nature of precision medicine, proposing proactive measures such as the establishment of multidisciplinary committees within the EU to adapt swiftly to emerging advancements and ensure seamless integration into healthcare systems. This symbiotic relationship between precision medicine and European law reflects a commitment to creating an environment where cutting-edge medical technologies can thrive, contributing to a healthier and more resilient population through ongoing efforts to refine legal frameworks.

**Keywords:** precision medicine, European legal frameworks, ethical considerations, healthcare policies.

# Ιατρική Ακριβείας στο Πλαίσιο του Ευρωπαϊκού Δικαίου: Ηθικές Παρατηρήσεις και Νομικές Προκλήσεις

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**Περίληψη**

Η ιατρική ακριβείας, που χαρακτηρίζεται από εξατομικευμένες στρατηγικές θεραπείας βασισμένες σε εξειδικευμένα δεδομένα που αφορούν συγκεκριμένο ασθενή, έχει κερδίσει έδαφος τα τελευταία χρόνια. Αυτή η αλλαγή από την παραδοσιακή προσέγγιση "one-size-fits-all" στοχεύει στη βελτιστοποίηση της υγειονομικής περίθαλψης ενσωματώνοντας πληροφορίες σχετικά με το γονιδίωμα του ασθενούς, του τρόπου ζωής και κλινικά αποτελέσματα. Ενώ ο αντίκτυπος της ακριβούς ιατρικής σε τομείς όπως η ογκολογία και η φαρμακογενετική είναι εμφανής, τα ρυθμιστικά πλαίσια, συμπεριλαμβανομένων του ΓΚΠΔ (GDPR), του Κανονισμού Κλινικών Δοκιμών, του Κανονισμού για τα in vitro διαγνωστικά και του πρόσφατα ισχύοντος(Ιανουάριο 2025) Κανονισμού Αξιολόγησης Τεχνολογίας Υγείας (HTAR), υπόκεινται σε λεπτομερή εξέταση για τις συνεισφορές και τα κενά που εντοπίζονται. Παρά την σημαντική πρόοδο, εξακολουθούν να υφίστανται προκλήσεις, όπως ζητήματα που σχετίζονται με την συναίνεση, τα συνοδευτικά διαγνωστικά τεστ, τα γενετικά τεστ, τα δικαιώματα πνευματικής ιδιοκτησίας και τις ποικίλες πολιτικές υγειονομικής περίθαλψης σε όλη την ΕΕ. Η έλλειψη παγκόσμιας εναρμόνισης προσθέτει πολυπλοκότητα στα ρυθμιστικά περιβάλλοντα. Τα συμπεράσματα τονίζουν τη δυναμική φύση της ιατρικής ακριβείας, προτείνοντας προληπτικά μέτρα όπως η ίδρυση διεπιστημονικών επιτροπών εντός της ΕΕ για την ταχεία προσαρμογή στις νέες εξελίξεις και τη διασφάλιση της απρόσκοπτης ενσωμάτωσης στα συστήματα υγειονομικής περίθαλψης. Αυτή η συμβιωτική σχέση μεταξύ ιατρικής ακριβείας και ευρωπαϊκού δικαίου αντανακλά τη δέσμευση για τη δημιουργία ενός περιβάλλοντος όπου οι προηγμένες ιατρικές τεχνολογίες μπορούν να ευδοκιμήσουν, συμβάλλοντας σε έναν πιο υγιή πληθυσμό μέσω συνεχών προσπαθειών για τη βελτίωση των νομικών πλαισίων.

**Keywords:** ιατρική ακριβείας, ευρωπαϊκά νομικά πλαίσια, ηθικές προκλήσεις, πολιτικές υγειονομικής περίθαλψης.

## 1. Introduction

Precision medicine (PM) is an innovative approach to treatment and prevention that utilizes large-scale data, including a patient's unique genome, environment, lifestyle, and biomarker information. Gaining popularity due to scientific advancements and political support, PM emphasizes a personalized approach within the doctor-patient dynamic. Unlike traditional personalized medicine, which simply tailored care to individual patients, PM leverages extensive individual-specific data to offer deeper insights beyond observable clinical signs and symptoms (1).

PM integrates genomics, proteomics, and metabolomics to analyze biomarkers in large sample groups or specific diseases. This approach combines standardization with individualization, aiming to fully understand a patient's genetic information to predict diseases and provide optimal prevention, diagnosis, and therapy. This enables healthcare providers to select appropriate medications, determine optimal dosages, and minimize side effects. The overarching goal of PM is to reduce major diseases' incidence, lower morbidity and mortality rates, enhance medical care quality through technological advancements, and ultimately improve human health (2).

The completion of the Human Genome Project (HGP) in 2001 revolutionized medicine by enhancing the understanding of genetics. Subsequent projects, like the International HapMap Project and the 1000 Genomes Project, continue to influence clinical practice, making DNA sequencing and big data analysis crucial for PM (3).

PM has shown significant potential in oncology and pharmacogenomics. In oncology, PM enables tailored treatment strategies based on the genetic and molecular characteristics of individual cancer patients, improving treatment effectiveness and patient outcomes. For instance, sequencing BRCA1 and BRCA2 genes helps assess breast and ovarian cancer risks. Trastuzumab, a monoclonal antibody, is prescribed for metastatic breast cancer patients with high HER2 gene expression (4).

As PM advances, examining the legal and ethical frameworks surrounding it is crucial, particularly within the European context. Large-scale databases, new patient classification methods, and advanced data analysis tools necessitate robust ethical, legal, and social frameworks. These frameworks must protect patients while fostering innovation and trust between patients and healthcare providers (5,6).

This article explores the intersection of PM and European law, addressing legal challenges, regulatory gaps, and ethical considerations. It aims to analyze European legal frameworks related to data protection, privacy, intellectual property, research ethics, and healthcare regulations, proposing recommendations to strengthen the regulatory framework.

## 2. Precision Medicine in Clinical Practice

### 2.1 Precision Medicine in Oncology and Pharmacogenomics

In the domain of oncology and pharmacogenomics, PM represents a revolutionary approach. It harnesses genomic and proteomic profiling, along with other biological traits of cancer, to pinpoint actionable mutations and biomarkers, aligning treatment strategies with these unique biological abnormalities. This all-encompassing concept spans molecular diagnostics, molecularly targeted therapies, next-generation sequencing (NGS), and immunotherapies. It originated with the discovery of single-gene mutations in certain cancer patient subsets, leading to the development of molecularly targeted therapies tailored to these genetic mutations. As PM has evolved, it now includes the analysis of multiple genes and comprehensive cancer cell DNA sequencing, in addition to immunotherapies designed to detect and combat cancer cells by modulating the immune system. Distinguishing itself from traditional approaches, PM tailors therapy to an individual's genomic mutations or biomarkers, promising enhanced treatment efficacy and reduced toxicity, thus signaling a transformative era in oncology and pharmacogenomics (7). PM in the context of cancer strives to deliver the appropriate

treatment, in terms of medication and dosage, to the specific patient at the optimal moment (8).

Pharmacogenomics (PGx) is the exploration of how genetic variations in genes responsible for drug metabolism and transport, impact drug levels at the intended site (pharmacokinetics), as well as in genes related to drug target proteins like receptors, enzymes, and intracellular signaling proteins, influence an individual's responsiveness to a drug (pharmacodynamics) (8).

Genetic testing and risk assessment constitute pivotal pillars in the realm of PM. Genetic testing includes the examination of an individual's genetic makeup to uncover specific genetic variants, mutations, or alterations associated with disease susceptibility or risk. This genetic information serves as a cornerstone for early disease detection, including rare genetic disorders. Moreover, this information plays an indispensable role in targeted therapies, based on an individual's genetic profile. Therefore, the possible applications of genetic testing encompass furnishing crucial information for patient or family care, diminishing the risk of illness or death, and offering insights for reproductive decision-making (9). These assessments provide healthcare professionals with invaluable insights into a patient's genetic predisposition, especially when it comes to rare diseases caused by single gene alterations.

Pharmacogenetic testing has also demonstrated efficacy in both reactive and preemptive settings, particularly concerning treatment response. Numerous studies highlight the cost-effectiveness of testing, which is significantly lower than addressing potentially life-threatening severe ADRs. To ensure the successful integration of pharmacogenetic testing, it is imperative to establish standardized implementation processes. Pharmacogenetic testing is on track to become a fundamental pillar in the realm of PM (10).

### 2.2. Role of Biomarkers in Diagnosis, Prognosis and Drug Response Prediction

A biomarker is a biological measurement that can be used as a substitute for, and ideally predict, a clinically significant outcome or a middle-stage result that may be harder to directly observe. Using clinical biomarkers is more convenient and cost-effective than directly measuring the final clinical outcome, and these biomarkers are typically assessed over a shorter period (11).

Biomarkers primarily serve as tools for key purposes such as screening, characterizing diseases, ruling out, diagnosing, staging, monitoring diseases, and offering prognosis information(11). An additional significant utility of biomarkers lies in their capacity to individualize therapeutic interventions by tracking the responses to treatments and forecasting treatment outcomes for specific patients (11). Biomarkers play a crucial role in the advancement of targeted cancer therapy, utilizing a range of targeted agents, including monoclonal antibodies (MoAb) (12).

Last but not least, in the evolving landscape of PM, the growing importance of biomarkers in pharmacogenomics is unmistakable. Notably, the FDA's compilation of a list of drugs linked to clinically validated pharmacogenomic biomarkers emphasizes their crucial role in customizing treatments (13)

## 3. Legal Frameworks in Europe

In the rapidly evolving landscape of PM, where tailored healthcare interventions depend on individualized patient data, robust legal frameworks are essential. This chapter explores the legal landscape governing PM in Europe, focusing on data protection and privacy regulations, intellectual property rights, research ethics, and informed consent.

### 3.1. Data Protection and Privacy Regulations

Since PM is based on individual characteristics, recognizing data sharing as a prerequisite for its successful implementation is vital, as it enables the collection, linkage, and reuse of diverse datasets encompassing molecular, clinical, phenotypic, and lifestyle information. The transformative potential of PM relies on the accessibility of data to multiple research groups, emphasizing the necessity for widespread sharing. This involves sharing both primary data, like human genome sequences, and secondary data previously utilized by original

collectors. Therefore, the necessity of a careful consideration of legal implications related to data sharing and privacy is crucial (14,15).

At the European Union (EU) level, in accordance with Article 168 of the "Treaty on the Functioning of the European Union" established in 2008, there is a dedication to guaranteeing a heightened level of safeguard for human health in all policies and undertakings within the EU. Additionally, the EU Charter recognizes the safeguarding of personal data, a subcategory of which are health data, as a fundamental right (14,16). The European Commission's recommendations in 2008 shifted their emphasis toward digital health and the cross-border interoperability of data. The objective was to outline guidelines for interoperable Electronic Health Records (EHR) and establish an integrated network for healthcare professionals and patients across EU, all in accordance with the fundamental rights of privacy and data protection (16).

The "General Data Protection Regulation" (GDPR) came into full legal force on May 25, 2018, applying to both the EU and the European Economic Area (EEA). This omnibus legislation establishes an all-encompassing legal structure designed to protect the personal data of Europeans and encourages conscientious handling of data for diverse valid objectives. GDPR brings about a substantial transformation in how organizations (hospitals, universities, research institutes, pharmaceutical industry) gather, utilize, and disseminate personal data (17). Its broad scope encompasses any data controller or processor, as well as any data subject located in the EU. Furthermore, the territorial scope (Article 3) of GDPR aligns with the data it safeguards, influencing the operations of organizations situated in various countries globally (14,17).

The primary goals of GDPR include protecting the data protection rights of individuals, particularly those participating in health research, and facilitating the "free movement" of personal data within the EU(17). GDPR outlines six key principles for handling personal information, emphasizing the importance of lawful, transparent, and fair processing. It requires explicit and legitimate purposes for data use, restricting reuse for other intentions. The regulation advocates minimizing data collection to what is necessary, ensuring accuracy and currency, limiting storage periods to original purposes, and enforcing secure data processing. The regulation empowers EU citizens with rights like access, consent withdrawal, data erasure, processing restriction, and prompt breach notifications (18).

The heightened transparency provisions of GDPR mandate that controllers inform data subjects, prior to processing and using clear language, about their intention to process the subject's personal data. Additionally, they are required to specify the lawful bases under Article 6 that justify the processing. In case of special category data (such as health or genetic data), controllers must identify the exception under Article 9(2) that allows for the processing of such data, since the processing of these special categories is generally prohibited (17). Specifically, Article 9 paragraph 2(j) states that data processing is allowed for scientific and research purposes, such as those required in PM. Additionally, "data concerning health" includes information derived from genetic testing, as clarified by Recital 35 of GDPR (17) .

Pseudonymized personal data, which are usually applied in clinical trials and scientific research, such as those key-coded, remain within the purview of personal data as outlined in GDPR. Pseudonymization involves a security measure that substitutes or eliminates information in a dataset that could identify an individual. On the contrary, the GDPR does not extend to anonymous data or data that has undergone anonymization. Anonymized data pertains to information that, when initially collected, was associated with an identifiable individual. However, through processes like scrambling or blurring that eliminate identifiers, the identity of the individual cannot be ascertained by reasonably foreseeable means. It is important to emphasize that the act of anonymization is recognized as a form of processing personal data (17). Anonymization techniques are usually used in research in case of data transfer, when the reconsent of the data subjects cannot be acquired.

In addition to individual country laws, there are universally applicable international laws like the "Universal Declaration of Human Rights" and the "European Convention on Human Rights", which emphasize the privacy rights of individuals, including the handling of personal information (18). Certain nations have also implemented extra security measures, beside those required by EU (19).

### 3.2. Intellectual Property Rights in Genomics Data

Intellectual Property Rights (IPR) can be understood as property rights, primarily involving intangible assets that safeguard innovations and creative works, serving as a reward for inventive and imaginative endeavors. IP law is guided by two fundamental principles: first, to ensure the public enjoys the advantages of IP, and secondly, to control and supervise competition in this domain (20).

Recent advances in biotechnology, particularly in molecular biology and genetics, have led to transformative changes in society, especially in medicine and healthcare. Gene sequences and their expression patterns, given their ability to enhance the identification and personalized understanding of various tumor types, have gained significant economic value when protected through IPR (19) . The convergence of biotechnology and IPR has opened up commercial opportunities, prompting industries to seek protection for biotechnological inventions. However, this intersection has presented unique challenges for IP laws. The conventional principles of IP laws have been expanded to encompass novel subjects like genes, proteins, and various single-celled and multi-celled living entities. These were previously excluded from the purview of IP regulations (20).

One of the most debated topics in discussions on biotechnology and IPR revolves around the eligibility of biotechnological inventions for patent protection. The conventional patent criteria, including patentable subject matter, novelty, non-obviousness (inventive step), utility (industrial applicability), and written description, face challenges when applied to biotechnology inventions, particularly those related to genetics. Human genes, in particular, have emerged as a highly contentious subject in patent law due to their diverse nature. Although there is a disparity in how member states of the EU handle patenting for biotechnology inventions, there are ongoing attempts to harmonize and unify patent laws. The European Patent Convention (EPC), which established in 1973, enables the submission and examination of a single patent application through the EPO. In 1998 the EU Directive 98/44/EC, commonly referred to as the Biopatent Directive, was adopted and serves as a supplementary tool for interpreting the EPC, providing additional guidelines and provisions, offering clarity to specific regulations regarding the patentability of biotechnological inventions, and addressing various aspects and potential ethical concerns associated with this field. Europe has outlined specific categories of subject matter that are either eligible or ineligible for patent protection in their respective legislations. Additionally, Europe incorporates a clause related to *ordre public* and morality to assess the patentability of biotechnological inventions (20).

On the global stage, the international patent framework faces challenges in addressing the new complexities introduced by biotechnology. This is primarily attributed to uncertainties and potential gaps within the text of the "Agreement on Trade-Related Aspects of Intellectual Property Rights" (TRIPS Agreement). The TRIPS Agreement establishes broad parameters for safeguarding biotechnological inventions, with Article 27.1 explicitly stating that patents should be granted for inventions in any technological field without discrimination, subject to specific conditions. This provision provides a legal basis for biotechnology patents, including gene patents, and imposes an obligation on member states to accommodate biotechnological innovations.

Beyond legal consequences, patents on genes and gene fragments carry substantial social and policy implications. These ramifications pertain to the accessibility of genetic research tools, advancements in genetic innovation, healthcare policies, the rights of patients, clinical practices, and the broader societal impact. The patenting of genetic testing, particularly in the diagnostic

realm, has become a contentious issue. Thus, diagnostic tests based on purely natural principles or phenomena cannot be patented (19,20).

The realm of IPR is continually broadening, with the regular emergence of new rights or the application of existing ones to relatively novel subjects, including genetic databases and human genes (20). A complicating element arises from the potential existence of additional IPR with data. In EU (excluding Switzerland), the protection afforded by copyright is supplemented by the sui generis regime specifically designed for databases (21). EU introduced the "European Database Rights Directive" to standardize protection across its member states. This directive safeguards a "collection of independent works, data, or other materials arranged in a systematic or methodical way and individually accessible by electronic or other means". Consequently, a database developer has the right to prevent the extraction and/or reuse of the entire or a substantial portion of the database's contents. However, it's important to note that the protection granted under this directive is restricted to individuals or legal entities residing in the EEA or in countries with similar protection mechanisms (20).

In order to address disparities in IPR, due to lack of harmonization between various jurisdictions, standardized contractual arrangements can be employed to delineate the rights of each involved party. In the field of biomedical research, Material Transfer Agreements (MTAs) are commonly utilized to regulate the sharing of human tissue and data among institutions, ensuring clarity regarding provenance (21).

### 3.3. Research Ethics and Informed Consent

Clinical research and trials necessitate a comprehensive, multi-faceted strategy. It goes beyond merely identifying and approving new drugs. Effectively managing a rare disease or cancer, for example, involves conducting intricate clinical investigations that combine drugs, companion diagnostics, advancements in surgical techniques, and novel radiotherapy approaches. Crucially, the integration of all available information, including biological samples and the growing significance of extensive data through big data technologies, is imperative(22).

EU has established a robust framework for clinical research, drawing upon ethical principles articulated in foundational documents such as the Helsinki Declaration, the "International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use - Good Clinical Practice" (ICH GCP), the Oviedo Convention, as well as principles enshrined in Human Rights and the Nuremberg Code. This framework encompasses key legislative instruments including the Clinical Trials Regulation 536/2014, the Directive 2004/23/EC regarding human tissues and cells, the Directive 2002/98/EC regarding human blood and blood components, the Regulation (EU) 2017/746 on in vitro diagnostic medical devices and the Regulation (EU) 2021/2282 on Health Technology Assessment (HTAR). Notably, the enforcement and governance of these regulations and directives are underpinned by GDPR, safeguarding personal data within the context of clinical research (22).

The Regulation 536/2014 addresses clinical trials on medicinal products for human use within the European Union. Key features of this regulation include a centralized EU portal and database for clinical trial information, a simplified application procedure, and a harmonized assessment process for multi-center clinical trials. The regulation emphasizes transparency, efficiency, and patient safety in the conduct of clinical trials.

The HTA Regulation, which is applicable from January 2025 onward, aims to enhance the accessibility of innovative health technologies, including medicines and specific medical devices, for EU patients. It promotes efficient resource utilization and elevates the quality of HTA throughout the Union. The framework establishes a transparent and inclusive structure, featuring a Coordination Group of HTA national or regional authorities, a stakeholder network, and rules governing the involvement of patients, clinical experts, and other relevant professionals in joint clinical assessments and scientific consultations (23,24).

GDPR delineates key provisions pertaining to scientific research. The establishment and roles of Data Protection Officers are detailed in Articles 37-39, while Articles 40 and 44-49 deal with codes of conduct and cross-border data transfers. Article 89 provides safeguards for processing personal data for scientific research purposes, offering a nuanced regulatory framework for the ethical and legal aspects of research within the GDPR (17).

In PM research, the management of information and data, particularly involving biospecimens and genetic details, raises critical legal and ethical issues related to consent and the privacy both of personal and familial health information (25).

The conditions governing consent have been strengthened to enhance data subjects' understanding of their consent regarding data processing, thereby reinforcing individuals' rights. The updated conditions for consent ensure that separate consent is required for distinct processing purposes in certain situations, and consent is deemed valid only if it can be withdrawn without any adverse consequences. It's crucial to note that consent represents just one of several legal bases for data processing under the GDPR. According to the GDPR (Art. 9(2)(a)), a request for consent must be presented distinctly, in an understandable and easily accessible manner, using clear and plain language. The specific purpose for processing, including sharing, should be clearly elucidated, and withdrawing consent should be as straightforward as granting it (17).

The primary objectives of informed consent within the Clinical Trials Regulation are threefold. Firstly, it aims to furnish comprehensive details about the study (e.g. duration, responsibilities and rights, associated risks, possibility of random assignment to control group) to ensure the participant is fully informed. Secondly, it addresses the future use of data, the disclosure of research results to participants, and the potential implications of unexpected and/or incidental genetic findings. Lastly, it emphasizes that patients, based on this information, make an informed decision on whether to participate in the study(19).

### 3.4. Healthcare Regulations and Reimbursement Policies

Healthcare regulations and reimbursement policies in the EU can vary among member states, as each country has its own healthcare system and policies. However, there are some overarching principles and frameworks that guide healthcare regulation and reimbursement in the EU.

- Regulatory Framework: EU has established a regulatory framework for medical devices, including in vitro diagnostic devices (IVDs). The “Medical Devices Regulation (MDR)” and “In Vitro Diagnostic Medical Devices Regulation (IVDR)” are key pieces of legislation that set standards for the approval and marketing of medical devices, including those related to precision medicine.
- Health Technology Assessment (HTA): HTA plays a significant role in the evaluation of the effectiveness, safety, and cost-effectiveness of healthcare technologies, including personalized medicine.EU has been working toward greater collaboration among member states in the field of HTA to ensure consistent evaluation and decision-making processes.
- Cross-Border Healthcare Directive: The “Cross-Border Healthcare Directive” allows EU citizens to access healthcare services in other member states and seek reimbursement from their home country. This directive may have implications for patients seeking PM treatments abroad.
- The “European Health Data Space (EHDS)” is an EU initiative designed to enhance the sharing of health data across member states. The primary goal of EHDS is to empower individuals by giving them control over their personal electronic health data and facilitating its secondary use. Additionally, EHDS aims to promote the development of a market for electronic health records (24).

PM has evolved from a research initiative to an established clinical concept. This transformation has elevated PM to a pivotal role, now acknowledged as an essential and integral component of the future of healthcare. This shift

in perspective has led to a strategic change, with PM transitioning from a primarily scientifically driven "bottom-up" development to a "top-down" approach. This new approach requires sustainable governance, comprehensive infrastructure, and stakeholder engagement, ensuring continuous research feedback and equal access to precision healthcare at regional or national levels (24).

Numerous European nations have made notable strides in integrating PM into their healthcare systems. The bottom-up approach is frequently grounded in regional networks, as observed in Sweden, Germany, and Italy. Conversely, the top-down method, involving government funding for national genome initiatives, has been implemented in countries such as England, France, Denmark, and Spain. There is a possibility that, at a certain stage, these two approaches may merge with established healthcare structures, providing an opportunity for national initiatives to complement existing systems (24).

Reimbursement policies for healthcare services and treatments, including PM, are determined at the national level, since each member state has its own healthcare system, financing mechanisms, and reimbursement policies (24). There are two reimbursement models that are used in PM, the traditional and the risk sharing ones. Conventional, non-risk-sharing reimbursement models are employed for the compensation of gene, cell, and targeted therapies, as well as biomarkers, genetic, and genomic tests in the healthcare sector. In Europe, confidential rebates are applied to payment models like Diagnosis-Related Groups (DRGs) (26).

Reimbursement for molecular diagnostic tests has been facilitated by integrating them into established payment models like DRGs and negotiated tariff-based payments at both local and national levels. This approach is observed in EU5 countries. Alternatively, the costs of diagnostics may be covered through allocations from state and hospital budgets or by pharmaceutical companies (26).

Lastly, healthcare reimbursement policies usually establish a "benefit basket," encompassing medical procedures, goods, and services that are eligible for (partial) reimbursement within the healthcare system. This benefit basket typically comprises one or more benefit catalogs, which are comprehensive listings of medical procedures, goods, or services. The catalog could adopt a positive listing, incorporating these procedures, activities, or goods into the benefit package, or a negative listing, excluding them. Descriptions of medical procedures in the catalog could either be generic (e.g., based on indication, test technique, or the biomarker under investigation) or involve a specific product reference within the procedure (27).

## 4. Ethical Considerations in Precision Medicine

Currently, the field of bioethics is advancing swiftly, blending the principles of science, medicine, law, and philosophy within the healthcare domain. Instances where ethical considerations do not necessarily align with legal permissibility prompt a discourse on revising laws to harmonize with the ethical dimensions of the issue (19).

### 4.1. Informed Consent and Patient Autonomy

Autonomy is a foundational principle in bioethics, crucial for informed consent in medical treatments or diagnostic procedures. Individuals are obligated to comprehend all pertinent information (associated risks and benefits) to make independent choices without coercion. Nevertheless, individuals must contemplate the extent to which their individual decisions should be honored in light of other individual considerations. This aligns with the harm principle, which supports respecting autonomy unless decisions significantly threaten others (19).

Over the course of several decades, safeguarding the autonomy of individuals involved in research and those contributing data has been contingent upon the principle of informed consent. Initially conceived as a mechanism for autonomous approval in research endeavors or medical procedures, informed consent has evolved to encompass various additional roles, such as delineating individual

preferences regarding data reuse and the disclosure of incidental findings (15).

Three forms of consent exist: explicit, implicit, and opt-out consent. Explicit consent involves presenting the purpose, use, handling, and disclosure of personal information, providing the option to agree or disagree—particularly vital for clinical trials and medical record retention, also known as opt-in consent. Implicit consent is assumed for both the data subject and collector, often evident during data collection (e.g., a doctor taking blood samples for lab tests). In opt-out consent, participants are informed about the purpose of consent with the choice to decline; if not declined, consent is considered provided (18).

The primary challenge associated with consent emerges during data sharing and linkage, a necessity in the data pre-processing phase of health data analytics, involving diverse sources like hospitals and insurance companies. Two consent approaches exist: static consent and dynamic consent. In static consent, approval is sought for all future data usage during collection, typically using paper-based methods. However, it lacks adaptability to changing environments and evolving requirements, such as repurposing data for different health projects not originally consented for. In contrast, dynamic consent offers advantages. It is an informed and personalized consent involving two-way communication between the data subject and custodian, allowing updates and various consent types. Additionally, the subject retains control over health data usage, with the ability to revoke consent through the interface. Notably, consent travels with the shared data, and participants gain access to research results (18).

In the context of obtaining consent from minors or individuals unable to provide consent, specific safeguards are in place. The involvement of parents or duly authorized individuals in decision-making on behalf of minors necessitates a careful consideration of the minor's best interests, with due attention to preserving their individuality. It is crucial to underscore that the objections raised by the minor/ person unable to consent must be honored, irrespective of the consent provided by their parents or authorized representatives (19).

Ethical concerns about patient autonomy arise with incentives for research participation, such as payments or gifts. Evidence shows economic incentives boost participation, but socioeconomic factors can introduce bias. Participants should possess a clear understanding of the conditions governing partial or non-payment. Typically, incentives should be set at a level that avoids exerting coercive or undue influence on the decision-making process regarding study participation. These incentives may include coverage for transportation, meals, and compensation for lost work hours during visits (19).

### 4.2. Data Privacy and Security

Balancing personal privacy with rights to healthcare, a healthful environment, and the judicious utilization of public funds poses ethical challenges in data privacy and security. EU health research follows a strong ethical framework with verified data handling protocols. Ethics committees evaluate risks and benefits, ensuring data use is proportionate to societal benefits. (28).

The main methods for ensuring data privacy encompass anonymization and pseudonymization. Anonymization includes randomization, which breaks direct data-individual links by altering data integrity, and generalization, which dilutes data attributes by using broader categories, such as "region" instead of "street" and ranges of years instead of specific years. Despite employing diverse methods in anonymization, it has been demonstrated that these techniques are not adequate to ensure privacy (18).

Pseudonymization involves substituting one attribute in a dataset with another to diminish the linkability between the original identity of a data subject and the dataset. Various techniques are employed for pseudonymization, including encryption with a secret key, the use of hash functions, keyed-hash functions with stored keys, deterministic encryption, and tokenization and masking (18).

Finally, the ethical imperative of minimizing the risk of information leakage or potential breaches is also of critical importance within the domain of data privacy and security.

4.3. Ethical Issues in Genetic Testing and Risk Assessment

Within the realm of in vitro diagnostic tests, genetic testing emerges as a crucial player influencing therapeutic decisions and personalized interventions. The two primary categories of genetic testing are Laboratory Developed Tests (LDTs) and genetic test kits. LDTs, prevalent in practice, originate within specific laboratories where patient samples undergo analysis, constituting a form of in-house genetic testing. Conversely, genetic test kits encompass a bundle of reagents and analytical information marketed to multiple testing laboratories. Noteworthy are the instances of certain genetic tests directly reaching consumers through Direct-to-Consumer (DTC) channels, a phenomenon that sparks considerable ethical discourse (25).

Challenges in genetic decision-making stem from the intricate nature of genetic mechanisms and their interactions with environmental factors, creating uncertainty about genetic disease causes and limited patient information. This complexity affects informed consent and necessitates careful consideration, as individuals may face significant decisions regarding family planning, including pregnancy continuation or termination, and prenatal diagnosis (29).

Safeguarding privacy in genetic testing requires careful attention due to the implications for both individuals and their family members. Disclosure decisions should consider the condition's severity, availability of effective treatments or preventive measures, and diagnostic reliability. Balancing patient confidentiality with third parties' autonomy over relevant genetic information is crucial, emphasizing the ethical complexity of sharing genetic data against individuals' wishes (29).

Prenatal diagnosis detects hereditary, infectious, iatrogenic, or environmental conditions, significantly influencing reproductive choices by providing fetal insights before birth. It is conducted not on the individual seeking the examination but on the conceived fetus, and impacts personal and familial aspects. Result communication should be within a non-directive counseling framework, respecting the autonomy of the pregnant woman and couple (29).

Finally, genetic information obtained through genetic testing, including increased susceptibility to future diseases, disorders, or conditions, should not be exploited for genetic discrimination. For example, the possibility of utilizing such information to deny employment based on an individual's predisposition to current or prospective medical issues has prompted numerous countries to implement legal measures (19).

In the contemporary landscape, the prevalence of easily accessible direct-to-consumer genetic testing (DTC GT) on the internet is on the rise. These tests, being products of PM, gather both potential risks and benefits (19).

Several challenges arise, encompassing a broad range of ethical issues. These involve concerns such as insufficient or problematic engagement of healthcare professionals, the effectiveness of pre- and post-test counseling, the scientific validity and utility of the testing, the insufficient interpretation of the results, deceptive advertising practices, the potential strain on healthcare systems, illicit testing in minors or third parties, the secondary use and privacy of consumer data, nonconsensual utilization and commercialization of testing, and regulatory issues related to DTC GT. Moreover, recent literature suggests that ethical concerns related to DTC GT remain unresolved. These issues have the potential to become more pronounced as the technology continues to evolve, and the range of services offered expands (30).

## 5. Regulatory Gaps and Challenges

PM offers significant advancements in diagnosis, treatment, and disease prevention. However, it faces regulatory challenges including data protection, privacy issues, and the need for standardized consent mechanisms. Ethical considerations such as equitable access and potential biases are also significant. Non-scientific barriers like regulatory hurdles, high development costs, and the need for extensive stakeholder collaboration further hinder progress.

Regulatory Uncertainty

Currently, regulatory uncertainty remains a notable challenge in PM R&D and implementation. The central problem is that certain current regulations seem unsuitable for PM, experiencing a lack of harmonization that currently hinders the progress of PM development (25). Moreover, the absence of harmonized procedures for the constituent elements of PM contributes significantly to uncertainty in regulatory approval (31).

Informed Consent

For many years, safeguarding the autonomy of research participants and data contributors has hinged on the concept of informed consent. Over time, informed consent has taken on additional roles, such as articulating individual preferences regarding data reuse and the disclosure of incidental findings. This expansion has resulted in a functional overload. While informed consent remains a vital prerequisite for utilizing secondary data, the current practices do not provide the necessary level of detail for data contributors to exercise meaningful control-especially concerning the diverse data types essential for PM (15).

The extent of informed consent in the context of PM, in particular, is intricate and significant. Typically, agreeing to participate in research involving an individual or their tissues pertains to a specific research activity that can be clearly outlined, allowing for meaningful consent or refusal based on an understanding of associated risks and alternatives. A challenge within the PM research domain arises from the question of whether a patient can provide a generalized consent for future research without knowledge of the specific nature and risks of that research. Often in PM there is a requirement to reassess tissue samples for research outcomes different from the initially specified purpose. Obtaining re-consent from tissue donors for an altered research objective may be impractical or impossible, and the necessity for such re-consent in all situations remains unclear (25).

Clinical Trials

While clinical trials play a crucial role in ensuring patient safety, many observers have suggested that they pose a significant obstacle to the prompt and efficient translation of research into therapy, particularly in PM. There exists a profound tension between the goals of PM, which aim to provide tailored therapies for smaller, stratified patient populations, and the standard clinical trial designs that evaluate efficacy in large and generalized patient cohorts. Initially, smaller clinical trial formats yield less compelling evidence regarding safety and effectiveness because of the limited patient pool involved. These compact trials lack the statistical robustness required to identify efficacy, particularly when the anticipated effect size is minimal. Additionally, in the absence of a comprehensive study involving a large, representative population, it becomes challenging to comprehensively assess the drug's benefit-to-risk ratio (25).

Data protection

Related to the data protection, the issue of data ownership arises in connection with collections of health information. These collections involve various stakeholders, each possessing distinct rights to their data (21).

As previously noted, conventional de-identification and pseudonymization techniques fall short in adequately mitigating the risk of re-identification. This risk is especially heightened when handling clinical and omics data (21). Ensuring data security and privacy for data-in-use presents a challenging task since it involves data computation (18).

Companion Diagnostics

An additional challenge encountered within the domain of PM pertains to Companion Diagnostics, which are predominantly used for in vitro assays or genetic tests, and are typically subject to regulatory oversight as medical devices (25). In the field of PGx, the primary focus lies on predicting the outcomes of drug interventions. The challenge with CDx is that the current reimbursement policies often do not support the synchronization of decision-making for both components. This discrepancy is attributed to historically divergent pathways for reimbursement decisions between in vitro diagnostics and medications. Consequently, this misalignment frequently results in the

reimbursement of the medication without corresponding reimbursement for the CDx. The lack of simultaneous reimbursement decisions can lead to suboptimal clinical decisions, potentially hindering the value of precision medicine practices (27).

Policy makers

For policymakers, the driving factors endorsing PM encompass the establishment of health policies that are secure, efficacious, and transparent, as well as demonstrating fiscal responsibility in health expenditure and safeguarding patient rights. Challenges and gaps are commonly arisen from a restricted comprehension of patient viewpoints regarding test utilization, insufficient awareness of the effects of testing on health efficiencies and outcomes, and conflicting priorities in health policy issues that may not prioritize the impact of testing, as well as inadequate supervision of diverse insurance and reimbursement schemes (31,32). Moreover, there is a lack of understanding of the clinical research needs, with legislation primarily concentrating on healthcare or product commercialization rather than clinical research. Despite the regulations pertaining to clinical trials, IVDs, medical devices, and data protection, this siloed approach may render the overall framework inconsistent and potentially detrimental to the EU's ability to advance swiftly in the realm of PM (22).

## 6. Recommendations for Improving Precision Medicine Regulations

The emerging challenges stemming from informed consent and data protection necessitate innovative technological solutions. Emerging digital consent technologies alleviate the burden on data donors by eliminating the need for intricate upfront decisions, enabling a more flexible, case-by-case consideration throughout the diverse applications of the data. For instance, innovative cryptographic techniques and decentralized ledger technologies like blockchain have recently emerged as potential avenues for enhancing the security of health data (15).

In addition, ensuring the security of physical devices and critical infrastructures (healthcare facilities, cloud servers etc.) is imperative. The implementation of a robust secure data backup system becomes essential to facilitate data recovery in the event of risks or system failures. Additionally, conventional access control mechanisms play a pivotal role in data security by regulating user access to sensitive information. Multi-factor authentication, like passwords, biometric scans, cryptographic tokens, and RFID cards, stands as a standard approach within access control. Intrusion Detection Systems (IDS) and Intrusion Prevention Systems (IPS) can serve as crucial components in bolstering security (18).

To address the challenge of data ownership, any viable solution must take into account not only data protection laws and research ethics regulations but also IP laws, including copyright, as well as agreements related to data use or material transfer (MTAs) (21).

Last but not least, propelling PM to the forefront demands a holistic approach that addresses several critical facets. Interoperability of frameworks stands as a linchpin, fostering seamless integration and collaboration across diverse systems. Equally crucial is the imperative for policymakers to be well-informed about the ever-evolving landscape of PM, underscoring the need for continuous education and awareness. Establishing multidisciplinary committees in policy-making endeavors ensures a comprehensive understanding of the multifaceted challenges and opportunities. Furthermore, engaging all stakeholders, from healthcare professionals to patients, industry leaders, and researchers, is paramount to cultivate a collective vision for the advancement of PM. Finally, an unwavering commitment to vigilance for advancements is essential to keep pace with the dynamic nature of the field, positioning EU as a trailblazer in the relentless pursuit of groundbreaking achievements in PM.

## 7. Conclusions

The exploration of PM has illuminated the profound impact of it across various medical fields and its evolving relationship with the legal frameworks within EU. The identified key findings also underscore its future perspectives,

particularly the promising advancements in cell and gene therapies.

The identified regulations within the EU represent significant strides toward creating a legal infrastructure for PM. However, gaps exist in the legal framework and the various healthcare policies and reimbursement models within EU, as well as worldwide.

Acknowledging the evolving nature of PM, there is a pressing need for proactive measures to address current and potential gaps. The establishment of multidisciplinary committees or a competent body in EU dedicated to PM can play a crucial role in promptly adapting to new advancements, ensuring patient safety, and facilitating the seamless integration of PM applications into healthcare systems. Finally, the symbiotic relationship between PM and European law is evident, recognizing both the potential and the challenges that come with the integration of cutting-edge medical technologies into legal frameworks. The ongoing efforts to bridge the gaps and proactively address emerging issues reflect a commitment to creating an environment where PM can thrive, benefitting individuals and society as a whole.

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