POSITION PAPER

Precision Medicine and the Appropriateness of Pharmacological Prescription

Increasing the Efficacy and Safety of Care as a Primary Tool for Pharmaceutical Governance and Sustainability

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Table of Contents

Foreword **2**
Executive Summary **3**
1. Introduction **8**
2. Prescriptive Appropriateness **9**
2.1 Prescriptive Appropriateness in Polypharmacotherapy: Drug-Drug Interactions 10
2.2 Polypharmacy and Multimorbidity: Improving the Prescribing Process in Geriatric Patients 13
3. Tools for Improving Prescribing Appropriateness **16**
3.1 Medication Reconciliation, Pharmacological Reconciliation, and De-prescribing 16
3.2 Software for Pharmacological Interaction Analysis 20
3.3 Pharmacogenetics and Pharmacogenomics 22
3.4 *Therapeutic Drug Monitoring* 31
3.5 Multidisciplinary approach and telemedicine **32**
4. Indicators of prescribing appropriateness: tools for patient centered medicine **32**
5. Prescribing appropriateness and correct use of medicines: from the patient's perspective **34**
5.1 Participatory medicine: involving patients in the care process 34
5.2 Adherence to therapies 39
5.3 Correct use of medicines by the patient: risks of self medication 40
6. Research priorities: Artificial Intelligence and Bioinformatics for Precision Medicine **41**
6.1 What is Artificial Intelligence in Precision Medicine? 42
6.2 Bioinformatics as the architecture of biomedical knowledge 44
6.3 Predictive algorithms 47
6.4 The need to create an Italian predictive model 52
6.5 Research priorities for the future 55
6.6 Training Pathways: the key to supporting the precision medicine ecosystem **57**
Appendix 1. Example of in silico simulation **59**
Appendix 2. Algorithmic Architecture of Clinical Prediction **62**
Random Forests and Gradient Boosting 63
Recurrent Neural Networks (RNNs) and Transformers 63
Bayesian Networks 64
Generative Adversarial Networks (GANs) 65

Foreword

A Wall Street Journal article published in 1999, titled "New Era of Personalized Medicine: Targeting Drugs for Each Unique Genetic Profile," contributed to spreading, on the wave of enthusiasm generated by the Human Genome Project (completed in 2003), the idea that we were facing an imminent evolutionary leap in medical sciences, based on the possibility of personalizing therapies (target therapies) according to the genomic profile of each individual. While it is true that today pharmacogenomic science, born from the genome project, contributes in various fields to choosing therapies more appropriately, it is equally true that the initial expectations of genomic-based personalization have been somewhat diminished due to factors of an economic nature (possibility of performing genomic tests in a cost-effective manner), clinical nature (availability of guidelines and evidence), technological nature (management and interpretation of highly complex data), and regulatory nature (privacy).

However, the idea of "personalization" of therapies has stimulated the scientific and broader community to address the issue of "appropriateness" of therapies in a new and holistic manner, placing not just the "disease" but rather the binomial "patient-disease" at the center of care strategies, and considering it as a unique entity that should be evaluated from a 360-degree perspective and treated following a diagnostic and therapeutic pathway where pharmacogenomics is only one of the many factors at play.

Although the more nuanced definition of "Precision Medicine" (PM) has been adopted over time in place of "Personalized Medicine," the clinical model proposed aims to act on all factors that contribute to the safety and efficacy of care. These are not only of individual and clinical nature, but also of an organizational, cultural, and social one. The goal is to create a functional health ecosystem in which two fundamental aspects are integrated:

- The systematic introduction of innovative tools typical of PM, such as pharmacogenomics (and more generally the characterization of patients at the molecular level), therapeutic drug monitoring, in-depth analysis of drug-drug and drug-food interactions;
- The re-evaluation of basic health and medical activities, starting from the accessibility of services and the physician-citizen communication, which impact the effectiveness of preventive interventions, the patient's active participation in care choices, adherence and compliance, as well as the correct use of medicines. New technologies should be leveraged to facilitate and track these activities, which is a prerequisite for the effective integration of available PM strategies into daily diagnostic and clinical routine.

In this scenario, the rationalization of pharmacological prescription processes according to PM principles will make it possible to trigger cascading improvements in the health system, impacting the patient's active involvement, the reversibility/progression of disease, and the economic and social costs (direct and indirect) derived from the disease.

Drug Regulatory Agencies, in their capacity as entities responsible for pharmacovigilance, monitoring of appropriate medicine use, and governance of pharmaceutical spending, have the task of actively contributing to this change, making PM strategies accessible and ensuring their correct incorporation into the workflows involving prescribing physicians.

With this document, AIFA intends to outline areas of improvement in prescribing practices, proposing actions consistent with configuring an improved system for managing pharmacological therapy, adequate to respond to the need for increased health also in a limited resources setting.

This paper aims not only to contribute to decision-making in the health sector but also to provide guidance for prescribing physicians and patients, guiding and including them in the paradigm shift currently underway in health systems.

Executive Summary

Precision Medicine adopts a methodology aimed at a multidisciplinary evaluation of the patient, including not only clinical assessment but also the evaluation of environmental, social, cultural, and emotional aspects that influence their attitude toward disease and care. In this context, the prescriptive process assumes the characteristics of a "-omics science," that is, capable of studying systems in their entirety, and becomes "prescriptomic." Implementing prescriptomics is equivalent to providing concrete tools for improving prescriptive appropriateness, through strong coordination and synergy between health stakeholders. The priority lines of action are indicated below:

- **Encourage, systematize and monitor therapeutic recognition, therapeutic reconciliation and de-prescribing activities**
    - *Opportunity:* Therapeutic recognition allows knowledge of all active ingredients taken by the patient (including those contained in over-the-counter products, supplements, herbal products, foods or beverages) and is particularly useful in the case of patients in care transition or under the care of multiple specialists. It allows identification and correction of prescribing errors and administration errors.
    - *Barriers/threats:* The time required for information gathering is limited, forcing the choice toward omitting this activity, especially in the absence of tools supporting decision-making, which would allow effective pharmacological reconciliation; limited communication with other specialists caring for the patient limits the multi-disciplinary comparison necessary for a complete risk-benefit evaluation with respect to modification of ongoing therapy.
    - *Corrective actions:* Standardize the forms used, make them digital and interoperable, so as to allow (i) consultation from different access points to patient care and (ii) continuous updating during an often fragmented care pathway; this flow minimizes the time required for pharmacological recognition and allows monitoring the use of a recommended practice. Identify "hotspots" in which the organizational environment and/or technological resources (hospitals, clinics, health centers) facilitate recognition and reconciliation activities, also by identifying actual reference centers that provide multidisciplinary pharmacological consultation assisted by bioinformatics/artificial intelligence.

- **Disseminate the use of simple tools for improving the efficacy and safety of pharmacological therapies**
    - *Opportunity:* Scientific literature offers a multiplicity of data suggesting that the use of simple tools such as assessment scales, predictive algorithms, questionnaires, can be effective in identifying problems related to pharmacological therapy, from clinical and pharmacological risk (e.g., STOPP/START criteria in the geriatric area) to non-adherence/persistence. Systematic use of these low-cost tools has the potential to prevent therapeutic errors and misuse of medicines, improving daily prescribing practices in a substantial portion of patients.
    - *Barriers/threats:* Knowledge of these tools is fragmented and often left to personal initiative. Many online resources are available in English only.
    - *Corrective actions:* In synergy with relevant scientific societies, select validated and most useful tools, providing guidance for use and recommendations regarding clinical actions to be implemented based on results obtained. Identify institutional reference websites through which to access the complete list of available tools, divided by area, and obtain appropriate information material (handbooks, manuals, guidelines); develop Italian versions of the online software. Leverage the new roles of pharmacy services to monitor compliance with prescribed therapies in a capillary manner.

- **Provide modern tools for preventive analysis of drug-drug interactions and promote a new role for clinical pharmacologists in healthcare**
    - *Opportunity:* Bioinformatic support tools (CDSS) are available, accessible from any electronic device, allowing to intercept in a capillary manner, on the territory, patients with high risk of ineffectiveness/toxicity linked to potential drug-drug interactions, initiating them into a therapeutic reconciliation pathway possibly supported by pharmacogenomic tests and therapeutic drug monitoring. Manage patients at pharmacological risk, identified by bioinformatic "screening," through expert pharmacological consultation, also performed via teleconsultation.
    - *Barriers/threats:* Insufficient training on the nature and actual clinical effects of drug-drug interactions detected by CDSS can lead to underestimation or overestimation of the risk associated with therapy, inducing inappropriate decisions and harming the patient (e.g., inappropriate discontinuation of background therapies on which the patient is stabilized to avoid a clinically minor or insignificant interaction). Inconsistencies in the methods of identifying and evaluating the severity of interactions between different software systems can lead to different decisions for the same patient.
    - *Corrective actions:* Invest in specific training programs (ECM courses, university master's programs, operational workshops) aimed at general practitioners, medical pharmacologists, clinical pharmacists and specialists, focused on understanding the biological bases and clinical effects of pharmacological interactions and training in the correct use of existing support tools for managing polypharmacy. Govern the process of using computational resources through the involvement of professionals experienced in the subject, because the evaluation of a DDI must be "multiparametric" and not simply based on the drug-metabolic interaction, largely and sometimes exclusively used by support software. This is possible by facilitating recourse to pharmacological consultation (possibly codifying it as an Essential Level of Care - LEA), identifying structures/reference centers where professionals specifically trained on the subject of pharmacological interactions can provide competent evaluation on complex cases, and leveraging remote communication systems. Furthermore, it is necessary to encourage the processes of clinical validation and regulate the acquisition of medical device certification for existing software/algorithms; promote a new role of clinical pharmacology (also through targeted training programs) in the proactive and reactive management of complex patients and therapies; encourage public-private collaboration programs aimed at developing, clinically validating, and certifying software and artificial intelligence systems that improve current performance and provide guidance for modifying polypharmacy to minimize the number of drugs administered and potential therapeutic problems.

- **Improve the methods for providing and using pharmacogenetic/pharmacogenomic data**
    - *Opportunity:* Obtaining the patient's pharmacogenomic map would make it possible to increase the level of precision and appropriateness of prescribed medicines in every phase of their clinical history, virtually accompanying them throughout their life (pharmacogenomic passport). Technological progress now makes it possible to analyze hundreds of DNA variants at the same cost or slightly more than what is necessary to analyze a few variants. We cite the concrete case of oncology patients, who largely receive prescriptions for tests for a few germline pharmacogenetic markers (established by the new Essential Levels of Care - LEAs), aimed at selecting only chemotherapy treatment. At substantially the same costs, obtaining a broader panel of pharmacogenomic markers in these patients would make it possible to optimize concomitant therapies assumed by the patient, which can interfere with the efficacy and safety of anti-tumor treatment.
    - *Barriers/threats:* Current LEAs do not provide for the possibility of reimbursing a broad pharmacogenomic panel, nor some markers currently used in clinical practice and generally recognized as useful, which would favor recourse to private facilities. Uncontrolled prescription of pharmacogenomic tests can negate the resource savings obtained by improving therapies in

accordance with the patient's pharmacogenomic profile. Insufficient familiarity with the type of test, with the varying modality of data reporting, with the phenotypic correlates of a pharmacogenomic marker, can lead to serious prescribing errors, such as failure to administer a necessary drug.

- *Corrective actions:* Update the LEAs by inserting new codes, identifying indications for prescription that do not exclude categories of patients in which tests can have greater benefit. Identify selection criteria for patients for whom it is appropriate (and reimbursable) to prescribe a complex pharmacogenomic panel (multigenic), also defining minimum content for such panels; issue recommendations aimed at standardizing the method of reporting pharmacogenomic markers. Publicize existing guidelines on the management of patients presenting pharmacogenomic markers, for example through one or more constantly updated institutional websites. Plan training and information for doctors and patients so that data are correctly used and interpreted. Consider the possibility of identifying reference centers for pharmacogenomic testing: the nature of the biological sample used for tests allows storage at room temperature and delayed shipment.

- **Conduct a census of the national network of TDM (Therapeutic Drug Monitoring) services and promote the issuance of shared guidelines**
  - *Opportunity:* TDM makes it possible to detect deviations in drug concentration in the blood compared to the concentration expected after administration of a given dose, identifying cases in which the prescribed dosage is not appropriate for the individual patient (due to pharmacokinetic alterations not otherwise predictable). The diffusion of TDM, a rapid and low-cost method, would therefore make it possible to minimize or control the incidence of significant toxicity or ineffectiveness, through therapy adjustment.
  - *Barriers/threats:* Faced with a large number of drugs, belonging to various therapeutic classes, for which TDM tests are available (included in the LEAs), the supply of this service appears fragmented nationally, in both qualitative and quantitative terms. The lack, for many drugs, of consolidated guidelines for requesting TDM, can lead to dosage requests even for patients in whom it is not really necessary.
  - *Corrective actions:* Initiate a survey of TDM services at the national level, to provide doctors and patients with a detailed map of active facilities. The survey would also allow tracking the technologies used and the volume of samples analyzed, in order to plan any improvement of services. Promote the establishment of expert groups aimed at reviewing and further developing guidelines, especially for clinical areas where TDM use is more recent. Promote training and information of physicians on already existing guidelines.

- **Plan the implementation of a national Artificial Intelligence system for health purposes**
  - *Opportunity:* Govern the advent of Artificial Intelligence systems by preparing the technological, regulatory and training infrastructure at national level. Guide the implementation of the AI in the health sector by identifying guidelines in compliance with Italian (and European) legislation, with the territorial organization, the financing system and the methods of resource distribution of the Italian health system. Expected benefits do not only include our ability to prevent, diagnose and treat diseases, but also an increased ability to manage health resources.
  - *Barriers/threats:* Lack of strategic vision and poor coordination between development of computational capacity, ethical governance and training programming.
  - *Corrective actions:* Coordinate the various existing experiences and initiatives on the territory from the outset, creating a national platform for predictive medicine, built on a broad and interdisciplinary alliance involving Scientific Institute for Research, Hospitalization and Healthcare (IRCCS), university hospitals, research centers such as CNR and ENEA, universities and polytechnics, high-tech companies

active in the fields of bioinformatics and AI, regulatory bodies such as the Ministry of Health, AIFA and AGENAS, as well as patient representatives and active citizenship. The platform should be organized in interoperable regional hubs coordinated by a national center. The main task of this network would be to collect and harmonize clinical, molecular, genomic, radiological and behavioral data from various sources, making them accessible in de-identified and structured form for training predictive models, in full compliance with the European data protection regulation (GDPR) and with the FAIR principles, which require that data be findable, accessible, interoperable and reusable.

- **Adapt prescriptive appropriateness indicators and data collection and integration systems**
    - *Opportunity:* Establish an articulated system for measuring indicators that allows for systematic identification and correction of critical issues related to prescription and use of medicines, in terms of both clinical outcomes and resource use. Creating a national repository where information flows from different health sources converge and which integrates, for example, laboratory data, clinical data, data on prescription and dispensing of medicines, would constitute an enormous opportunity for extracting new scientific knowledge and increasing the managerial capacity of the health system, thanks to bioinformatic and AI-assisted data analysis.
    - *Barriers/threats:* Limitations to the interoperability of health information systems; economic investment needed to upgrade IT infrastructure; "defensive" attitude toward indicator measurement.
    - *Corrective actions:* Plan a progressive integration of information flows that allows diluting resources over time. Set up an indicator use program not as a tool for measuring and evaluating the work of the physician/health facility, but as a tool for identifying and correcting the causes and conditions that prevent achievement of objectives set by the indicators.

- **Encourage Participatory Medicine**
    - *Opportunity:* Re-establish the physician-patient alliance. Involving the patient in the care process through knowledge transfer can increase adherence, mitigate fears, allow recognition and management of possible toxic effects, and avoid errors in drug administration. Listening to the patient's narrative allows improvement of therapeutic choices, identification of critical issues and finding shared and acceptable solutions for the patient.
    - *Barriers/threats:* Scarcity of time available for physician-patient communication. The quantity and universal accessibility to partially or unverified information by citizens generates false expectations or unjustified fears, contributing to a climate of unjustified aversion toward health professionals and defensive medicine approach by the physician.
    - *Corrective actions:* Plan, in collaboration with medical and patient associations, information actions with capillary distribution (brochures, social media, authoritative reference websites) but also opportunities for direct discussion and in-person training, aimed at educating on appropriate use of medicines, real risks associated with medicine taking versus risks associated with non-adherence, limits and potential of pharmacological treatments, to increase patient awareness of the risk/benefit ratio and enable informed choice. Encourage the presence of patient associations at points of care, facilitating their offer of support services to both citizens and health professionals. Through specific training programs, promote the culture of communication in health professionals, understood as a communicative methodology that employs specific techniques.

- **Build a shared training and information network**
    - *Opportunity: Create a network of stakeholders capable of engaging the broadest audience of health professionals and patients-citizens. Transfer to health professionals the skills necessary to use old and*

new tools aimed at therapeutic personalization in an efficient and effective manner. Disseminate among citizens authoritative, updated and balanced information about the real possibilities of Precision Medicine. Create actual training courses (degree programs, doctoral programs, master's degrees, etc.) designed to create qualified professional figures capable of managing innovative activities that characterize the new frontier of healthcare.

- *Barriers/threats: Difficulty in coordinating between different subjects, public or private.*
- *Corrective actions: Creation or identification of a "condensation nucleus" composed of a few individuals, which triggers a cascade system of membership. Build and implement initially a few pilot projects, identified through assessment (survey) of training/information needs, potential impacts and feasibility. Pursue synergies through open "calls" aimed at sourcing candidates for specific tasks. Use dissemination of results obtained as a tool to attract further collaborations.*

- **Build a reference portal for Prescriptomics**
  - *Opportunity:* Facilitate access and usability of tools for improving prescriptive practice, by providing: (i) search functionality for facilities providing services such as therapeutic drug monitoring, pharmacogenomic tests, pharmacological and/or pharmacogenomic consultations and links to web pages indicating how to access services; (ii) links to free/licensed online algorithms for calculating clinical risk indices and pharmacological interactions; (iii) consultation on a single website of all relevant guidelines and recommendations in the field of prescriptomics, including those related to Gender Medicine; (iv) consultation of available training options (ECM, university courses, workshops, conferences, etc.); a page dedicated to citizens that collects educational and information material, giving space to initiatives promoted by and with Patient Associations.
  - *Barriers/threats:* No particular problems are detectable, except the risk of incompleteness of information due to the multiplicity of individual initiatives in the field of precision medicine, the proliferation of algorithms and predictive systems, the difficulty of censusing public and private diagnostic services throughout the national territory.
  - *Corrective actions:* Launch an information and dissemination campaign that invites healthcare facilities, scientific societies, medical and patient associations, academies, scientific institutes, to join the prescriptomics platform, establishing a mode of communication that allows continuous updating of platform content.

1. Introduction

The "Osservasalute Report 2023" produced by the National Observatory on Health in the Italian Regions indicates that 24.0% of the population residing in Italy has reached the age of 65. Specifically, 11.7% is aged between 65 and 74 years, 8.5% is aged between 75 and 84 years, and 3.8% (2.2 million citizens) is aged 85 or older. Increased life expectancy and progressive aging of the population are accompanied by an increase in the burden of chronic diseases, multi-morbidity, and intrinsic patient fragility.

The Italian Institute of Statistics (ISTAT) data report that in Italy 40% of the population (approximately 24 million people) suffers from at least one chronic disease, while approximately 20% suffers from two or more chronic diseases. Analyzing data for patients under the care of General Practitioners (MMG) included in the Health Search (HS) network, the "Osservasalute Report 2023" indicates that the following are among the prevalent chronic diseases: arterial hypertension (28.8%), thyroid disorders (excluding tumors) (17.1%), osteoarthritis (15.0%), asthma (9.0%), type 2 diabetes mellitus (7.9%), ischemic stroke (4.5%), ischemic heart disease (4.1%), obesity (3.0%), and COPD (2.7%).

Patients with multi-morbidity account for 49.2%, and among patients aged 65 or older, 68.0% have received prescriptions for at least five different substances (definition of chronic polypharmacy) and 28.5% for at least ten. Additionally, drug exposure is differentiated by gender, with a prevalence of 63.0% in males and 72.0% in females.

Concurrently, the "National Report on Drug Use in Italy," published by the National Observatory on the Use of Medicines (OsMed), indicates for 2023 a pharmaceutical expenditure borne by the National Health System (NHS) equal to 24.9 billion euros, with an increase of 5.7% compared to 2022. This figure accounts for 69.7% of total recorded pharmaceutical expenditure (36.2 billion euros).

The statistical data reported above immediately convey the dimension of the "prescriptive appropriateness" problem, which in the era of Precision Medicine assumes new connotations. The medicine is a tool to be used prudently and in an informed manner, both by the prescribing physician and by the patient. In fact, health problems related to medicine use, such as adverse reactions, pharmacological interactions, inappropriate dosing, off-label use and poor compliance, trigger a series of mechanisms and cascading events that determine high consumption of (already limited) resources and become a social problem. Toxicity, ineffectiveness, and poor adherence determine disease progression/lesser reversibility, further use of medicines and treatments, increased access to primary care and hospitalizations, diminished social functionality of patient and caregivers, with all the direct and indirect costs derived.

It is certainly not new in medicine, the concept of extremely variable response to treatments from patient to patient, as a result of the interaction of multiple factors: strictly clinical (diagnosis, comorbidities, etc.), pharmacological (interactions), demographic (age, gender), genomic, behavioral (lifestyle), environmental (exposure to risk factors). In seeking to predict and govern this variability, medical and diagnostic sciences have always sought new elements of stratification that would provide a basis for differentiating therapeutic choices. The innovation brought about by Precision Medicine consists in an enormously amplified ability to identify and evaluate old and new predictive factors of response in an integrated manner, thus increasing the "precision" with which therapies are selected for each patient, and therefore prescriptive appropriateness, which ensures greater probability of efficacy and lower toxic risk. It is now imperative, also from an ethical standpoint, to accelerate the transfer to society of technical-scientific acquisitions, such as complex germline pharmacogenomic tests, Clinical Decision Support Systems (CDSS) for prediction and prevention of pharmacological interactions, but also cultural acquisitions, such as the need to involve patients in decision-making processes concerning their own health. The era of rapid technological evolution we are living in constitutes the best substrate for putting current knowledge to fruit, providing communication, conservation, transfer, and processing systems of data unimaginable not long ago, with their maximum expression being in Artificial Intelligence (AI) systems.

However, "precision prescription" should not be considered a sophisticated system of limited use. Instead, it should be seen as a set of practices with increasing levels of complexity, to be applied in a differentiated manner and correctly dimensioned with respect to the clinical question, and to the context in which one operates. Planning the systematic

and coherent application of these practices requires actions aimed at disseminating critical knowledge about them, facilitating their use, identifying criteria for applicability, and evaluating their effectiveness and efficiency.

2. Prescriptive Appropriateness

Traditionally, a pharmacological prescription is considered appropriate if "performed within the clinical indications for which the drug has proven effective and within its indications for use (dose and duration of treatment)" (AIFA). Based on this definition, important initiatives have been carried out to guide and monitor the correctness of prescriptions, such as AIFA notes, therapeutic plans and monitoring registries, which have demonstrated their effectiveness in promoting the appropriate use of medicines.

Introduced in 1993, AIFA Notes constitute clear limitations on the use of a group of medicines, reimbursed by the health system, which have been identified as being problematic both from a clinical and from an economic standpoint since they are easily susceptible to misuse (presence of many clinical indications but with different degrees of significance and effectiveness). Similarly, AIFA Therapeutic Plans (TP) limit reimbursed prescriptions to medicines considered essential for a given disease, guiding physician choices toward the most effective medicines according to available evidence. Monitoring registries, established by AIFA in 2007, allow monitoring of the use of innovative and high-cost medicines (such as biological drugs), thus verifying the appropriateness of prescription to the therapeutic indication.

These examples validate an effective methodology common to other instances, such as antibiotic stewardship programs and the National Plan to Combat Antimicrobial Resistance (PNCAR) 2022-2025, characterized by:

- identification of an area critical for inappropriate use of medicines;
- clarification of the manner in which the physician verifies the criteria of appropriateness of prescription;
- tracking of prescriptions and consumption;
- verification of effectiveness through measurement of indicators and data analysis.

In the era of Precision Medicine, such approach should be extended by broadening the concept of prescriptive appropriateness, so that it includes the multiplicity of biological, clinical, behavioral, and social factors that today are recognized as additional indications and contraindications to medicine administration in a given patient. Therefore, prescriptive appropriateness should be articulated in multiple forms, identifying areas of specific improvement in light of the opportunities provided by advancement in technology, science, and socio-cultural aspects. Using a rating scale linking (i) size of the affected population, (ii) potential for impact on health and containment of healthcare expenses and (iii) feasibility of improvement interventions, the areas of priority intervention are clearly polypharmacotherapy and pharmacological treatment of the elderly patient (often in polypharmacotherapy) (see para. 2.2).

One can then identify cross-cutting areas of intervention that contribute to improving personalization of prescriptions, and respond to the ethical questions of modern medicine:

- **Gender Medicine (GM):** The (relatively recent) awareness of a considerable gender gap both in research and in clinical practice has stimulated the development of GM. The World Health Organization defines gender-specific medicine as the study of the influence of biological differences (defined by sex) and socioeconomic and cultural differences (defined by gender) on the health and disease status of each person. Gender Medicine has also highlighted how the female sex is under-represented in clinical trials, causing a methodological bias preventing observation of differences in drug efficacy and safety. Gender differences also translate into different susceptibility to disease onset, different disease progression and response to therapies, and sometimes in different sensitivity and specificity of diagnostic criteria currently applied. In addition, the diversity in lifestyles and attitude towards use and consumption of medicines is not negligible. It is a shared opinion that, with respect to evidence of biological, behavioral and social variance between genders, guidelines for gender-specific choices are currently lacking, despite a Ministry of Health Decree implementing Law 3/2018 - a "Plan for the Application and Dissemination of Gender Medicine in the National Territory" - was already approved in 2019.
- **Participatory Medicine (see para. 5.1):** It represents an approach that conceives the centrality of the patient not only as a unique biological entity, whose characteristics can guide therapeutic choices, but as an active and

aware agent of the care process, instrumental for therapeutic success. By translating this concept at social level, patient associations become health stakeholders who participate in decision-making processes within the health system. The relationship between Participatory Medicine and appropriateness of prescription may not be immediately apparent due to a cultural limitation that often sees the patient as a passive recipient ("object") of medical care, but becomes evident when medical prescription is harmonized with the needs, preferences, and beliefs of the "subject" being treated (see para. 5.1).

2.1 Prescriptive Appropriateness in Polypharmacotherapy: Drug-Drug Interactions

Polypharmacotherapy, generally defined as the simultaneous use of five or more medicines, is a frequent condition not only in the elderly population with multi-morbidity (para. 2.2), but also in particular categories of fragile patients, such as cancer patients and patients with neuropsychiatric disorders. This condition has been identified in itself as a risk factor for inappropriate prescriptions, drug-drug interactions (DDIs), and consequently adverse reactions. Interactions can occur during simultaneous or close administration of two or more medicines, and can result in a response different from that expected. It is known that the prevalence of DDIs increases with the number of medicines taken by the patient, but also in situations where there is poor control, such as in the case of medicine prescription by multiple physicians or specialists, transitions of care, or in the case of limited ability/possibility on the part of the prescriber to recognize an interaction.
Patients on polytherapy present a greater risk of toxicity and/or ineffectiveness caused by DDIs not only because of a greater number of interactions, but also because polytherapy patients are generally more fragile – they are often elderly people with comorbidities - and present clinical characteristics that can amplify the clinical effect of DDIs, making consequences more harmful and of more complex resolution.
The majority of DDIs occur at the pharmacokinetic and pharmacodynamic level. Pharmacokinetics is determined by the speed of the mechanisms that mediate Absorption, Distribution, Metabolism, and Elimination (ADME system). Therefore, it affects the amount of medicine available at the target site as well as the amount of circulating medicine, which can be transported and can produce biological activity at non-target sites. Pharmacodynamics is determined by the manner in which the medicine acts, for example by binding a receptor, and therefore affects its potency and effectiveness. Most pharmacokinetic and pharmacodynamic mechanisms involve the interaction of the medicine with a protein, which can act as a transporter between different compartments, as a metabolizing enzyme, or as a target/receptor of the medicine.
Enzymatic proteins that metabolize medicines are a prevalent component in the establishment of DDIs. The biotransformation of xenobiotics has a detoxifying valence, and in the case of medicines, the active ingredient is converted into a metabolite that can be more easily eliminated by the body. It is often inactive but sometimes can have a pharmacological action or can exert toxic action. Medicines undergo two main types of metabolism: Phase I, which includes oxidation, reduction, hydrolysis reactions, and Phase II, which includes conjugation reactions with endogenous molecules such as glucuronic acid, sulfate, methyl group, acetyl group. Among Phase I enzymes, the Cytochrome P450 (CYP450) enzymatic system plays a predominant role. It consists of a superfamily of enzymes composed of 18 families and 43 subfamilies for a total of 57 enzymes, some of which (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, 5, 6) interact with the majority of medicines. Individual CYP450 enzyme isoforms show broad binding specificity enabling them to catalyze different reactions on many different medicines, and are also susceptible to positive (induction) or negative (inhibition) regulation by a host of molecules, including many medicines. Thus, a scenario occurs in which multiple medicines administered simultaneously, acting on the same enzyme, alter the speed of catalysis and/or binding affinity with the substrate medicine, ultimately determining an alteration of pharmacokinetics, that is, the speed at which a given medicine is transformed into a metabolite.
To provide an example of the complex situation: amiodarone is a substrate of CYP3A4 and at the same time an inhibitor of CYP1A2, CYP2C9, CYP2D6, and CYP3A4 itself. This determines an interaction with co-administered medicines and substrate of the inhibited cytochromes, which may undergo an alteration of the expected concentration. To avoid the interaction, the individual medicines could be substituted with pharmacologically equivalent medicines that are not substrates of the inhibited cytochromes, or amiodarone itself could be substituted. Similarly, one could act in the case of combinations of medicines that are substrates and inducers of CYP450. Table 1 provides a list of web resources, including their corresponding links, where cytochrome P450 interaction tables can be consulted.

The same drug-protein-drug interaction mechanism can also occur at the level of drug transporter proteins, which exhibit similar ability to bind many different medicines and to have their activity regulated by others. Transporters,

classifiable into the three superfamilies ATP-Binding Cassette (ABC), Solute-Linked Carrier (SLC), and solute carrier organic anion (SLCO), transport the passage of medicines from outside to inside cells (influx transporters) or from inside to outside (efflux transporters) and are involved in the processes of drug absorption at the gastric level and elimination at the renal level. A noted example of clinical effect derived from a pharmacological interaction at the transporter level is pravastatin and rosuvastatin myopathy in co-administration with medicines that inhibit the SLC01 transporter, such as cyclosporine.

Table 1. Selected web resources for consulting information on substances interacting with the isoenzymes of the cytochrome P450 superfamily

Web resource	Description
http://flockharttable.org/	It allows you to search by drug and cytochrome and classifies the strength of the interaction (substrate, inducer or inhibitor) in weak, medium, strong. In English.
https://drug-interactions.medicine.iu.edu/MainTable.aspx	Provides tables of drug-cytochrome interactions (substrate, inducer or inhibitor). By clicking on the individual drug, more information on the interaction is available, including the possible presence of an FDA label related to the interaction (with a link to the document).In English.
https://www.msdmanuals.com/it/professionale/multimedia/table/sostanze-comuni-che-interagiscono-con-gli-isoenzimi-del-p-450	List of common substances that interact with P-450 isoenzymes. In Italian.

Regarding pharmacodynamic pharmacological interactions, they cause an alteration of the biological effect at a direct level, through agonist or antagonist-type interaction on the same receptor, or at an indirect level, by acting on different functional systems.

Based on knowledge of the dense network of drug-protein interactions, therefore, many DDIs can be anticipated and minimized by selecting the combination of medicines that presents the fewest interferences with ADME mechanisms and mechanisms of action of other medicines.

However, the clinical application of these principles is not straightforward. In polypharmacy, many individual drug-drug interactions occur on the same protein, and become significant only when the pharmacokinetic variation produces a variation in drug concentration such that it no longer falls within the therapeutic range, or results in the production of active/toxic metabolites such as to modify the clinical response. Therefore, it would be necessary to have adequate risk prediction systems in place associated with a certain pattern of pharmacological interactions, which also encompasses all those factors related to the patient that can amplify the clinical effect of a DDI, such as organ functionality, presence of comorbidities, gender, and presence of pharmacogenomic variations (see para. 3.3).

Uniformity in the classification of DDIs is a fundamental requirement to avoid discrepancies in the interpretation of DDIs that would induce, rather than limit, prescribing errors. The description of the severity of interactions is fairly widely shared and usually includes three levels:

- Mild interaction level: The combination of medicines presents interactions that have low probability of manifesting clinically or causing serious harm to the patient, and can be administered to the patient.
- Moderate interaction level: The combination of medicines can result in worsening of clinical conditions and it is appropriate to modify therapy or at least monitor the patient appropriately.
- Major (or severe) interaction level: The combination of medicines should be avoided because it is associated with high risk of serious harm to the patient.

Some bioinformatic systems are being developed and are available for the assessment of DDIs. However, they still show some limitations, including inconsistency in the criteria by which interactions are assigned to a risk class, and should therefore be used with attention and awareness (see para. 3.2).

It is extremely important that prescribers become familiar with the issue of DDIs and possible clinical consequences, and that they acquire the skills necessary to identify patients at greatest risk. Equally important is the creation of a system for providing pharmacological consultation services that then supports the physician in managing complex therapies in fragile and high-risk patients:

- Patients with multiple risk factors: Individuals with chronic diseases such as diabetes, heart failure, hepatic or renal insufficiency, multi-morbidity, and polypharmacy. Elderly patients commonly present all these characteristics, and their intrinsic fragility can exacerbate the effects of possible DDIs and adverse reactions.
- Patients undergoing pharmacological treatments with high toxic profile but at the same time life-saving and difficult to replace, such as cancer patients.
- Patients treated with polypharmacies including medicines with narrow therapeutic index and whose side effects can undermine both the social functioning of the patient and adherence to therapy, such as psychiatric and neuropsychiatric patients.

The peculiar problems of prescriptive appropriateness in the geriatric patient are addressed in the following para. 2.2.

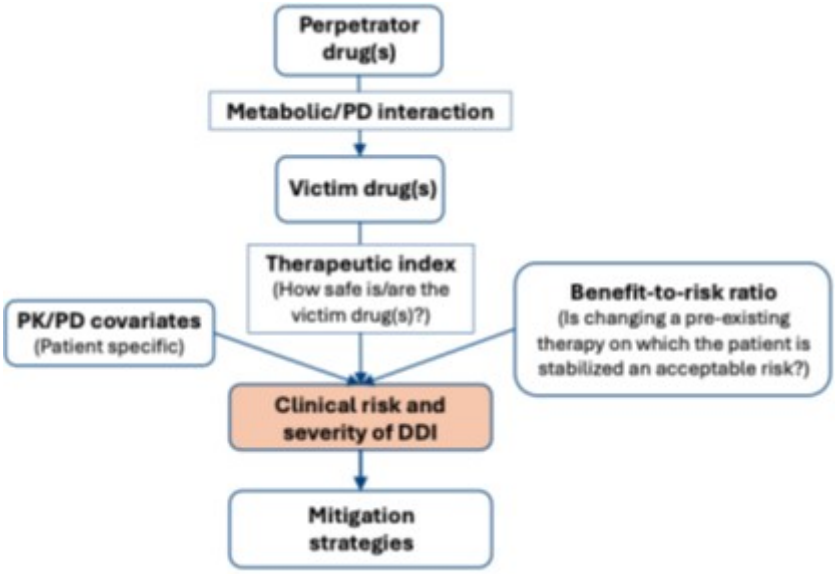
In cancer patients, even young ones, the need to manage side effects of anti-tumor medicines, such as nausea, vomiting, neutropenia, pain, frequently induces the administration of more than five medicines simultaneously. Despite the great attention placed by precision oncology in selecting the most appropriate medicine based on the molecular characteristics of the tumor, and in identifying in advance subjects exposed to serious risk of toxicity due to the presence of pharmacogenomic variants (para. 3.3), much less attention is placed on the selection of support medicines, or on adaptation of medicines for treatment of comorbidities, so as to minimize pharmacological interactions that could harm the level of efficacy and tolerability of the main chemotherapy treatment, and interfere with other treatments. A concrete example is provided by data from a recent meta-analysis on a sample of more than 6000 patients receiving VEGF-TKI medicines, showing how concomitant use of anti-acid has worsened oncology treatment outcomes in terms of survival, mortality, and disease progression.

In keeping with the increasingly recognized need to make oncological and non-oncological therapies compatible, the American Heart Association recommends careful evaluation of the profile of pharmacological interactions in cardio-oncology patients, providing recommendations on both monitoring and preferred cardiovascular therapy, differentiated based on the oncology treatment received by the patient.

A further area of high socio-health impact in which the correct management of polypharmacy shows high potential for improvement is that of psychiatric and neuropsychiatric treatments. In this area, the prescription of multiple medicines in the same therapeutic class or in different therapeutic classes is very frequent and presents peculiar problems: it often includes medicines with a narrow therapeutic interval (which expose to greater risk of ineffectiveness/toxicity); toxic effects, even cumulative, can be particularly severe; it can induce development of comorbidities; frequently treatment resistance develops.

It is therefore necessary to develop structured guidelines, in order to develop - where possible - real decision trees that guide the physician in the prescriptive process of complex therapies and in the monitoring and verification of prescriptive appropriateness. It is necessary to define clear (and shared) criteria to identify patients in whom it is advisable to proceed with the analysis of drug-drug interactions (see para. 3.2), the request for pharmacogenomic tests (see para. 3.3) or therapeutic drug monitoring (TDM, see para. 3.4).

A recent article published jointly between the Italian Association of Medical Oncology and the Italian Society of Pharmacology has contributed to defining the methods of assessment of DDI in oncology, as shown in the figure below.



2.2 Polypharmacy and Multimorbidity: Improving the Prescribing Process in Geriatric Patients

In Italy, the Aging Index, namely the percentage ratio between the elderly population (aged 65 years or older) and the young population (under 15 years), calculated on January 1st of each year, has been steadily increasing for over two decades. The general aging of the population is inevitably accompanied by an increase in multimorbidity, which often leads clinicians to use numerous therapeutic agents in the same patient. This phenomenon causes issues of no small importance and, particularly in the geriatric population, results in an increased risk of even severe adverse events, worsening of quality of life and general conditions, and even higher hospitalization and mortality rates. This is related to the appropriateness of prescriptions, which is not always fully satisfactory, the poor propensity for "de-prescribing," the erroneous intake of medications by patients with objective difficulties in managing complex therapy, the adverse effects of individual active ingredients—particularly burdensome when acting in a clinically fragile individual—and drug-drug interactions. The described scenario also entails high healthcare expenditure, both for the medications themselves and for hospitalizations that may have iatrogenic damage due to polypharmacy as a possible contributing factor.

To get an idea of the severity of the phenomenon, it suffices to consider that, according to the most recent data, the concurrent use of more than four drugs increases the risk of Adverse Drug Reactions (ADR) by about three times. The most frequently—and often inappropriately—prescribed drugs include proton pump inhibitors, psychotropic drugs (benzodiazepines, antidepressants, antipsychotics), diuretics, antiplatelets, and analgesics.

Some examples of specific contraindications existing for geriatric patients reveal the extreme need for personalized care in the elderly. Attention must be paid to prescribing dopamine antagonists such as antipsychotics but also commonly used antiemetics (e.g., metoclopramide) due to possible central adverse effects and, in patients with Parkinson's disease, due to possible worsening of motor symptoms; cyclizine, an antihistamine and antiemetic, can impair cognitive and psychomotor performance; domperidone and 5HT3 receptor antagonists increase cardiovascular risk; among bronchodilators, beta-agonists can induce tremors, exacerbated by possible co-administration with cholinesterase inhibitors; theophylline can lead to neurological adverse effects (headache, anxiety, behavioral disturbances); among analgesics, NSAIDs can cause delirium and psychosis, worsen the diuretic response in patients with heart failure, and blood pressure control in hypertensive patients; opioids cause sedation and constipation; among cardiac drugs, digoxin at therapeutic doses can induce nightmares and is associated with the onset of acute confusional states; particular attention must also be paid to prescribing drugs that may increase the so-called "anticholinergic burden" due to their known adverse effects on cognitive abilities in this class of patients.

In conclusion, the management of polypharmacotherapies, which is inherently insidious, requires further attention in the elderly, where the physician must evaluate a series of additional risk factors, among which the following are particularly relevant:

- Greater susceptibility to adverse drug events. The aging process itself involves physiological changes that determine modifications in pharmacokinetics and pharmacodynamics: intestinal absorption is altered due to lower gastric acidity, reduced gastrointestinal motility, and lower intestinal blood flow; drug distribution is disturbed by increased fat mass and corresponding reduction in lean mass, so the volume of distribution of liposoluble drugs is increased and that of hydrosoluble drugs is reduced; renal clearance is reduced with consequent increase in the half-life of drugs eliminated renally; hepatic metabolism is also less efficient with z consequent increase in the concentration of drugs with high hepatic clearance; sensitivity of target tissues is altered due to qualitative and quantitative changes in the number of receptors for individual active ingredients; the presence of chronic diseases is finally a factor that in itself can alter the response to drugs.
- Degree of patient frailty. Frailty can be defined as a condition of considerable vulnerability of the individual to stressful factors, whether endogenous or exogenous, and is caused by exhaustion of age-related homeostatic reserves. The frailty construct is linked to a dual framework: the first is the Frailty Phenotype, suggested by Linda Fried and colleagues in 2001 and based on the identification of five clinical signs or symptoms (weight loss, fatigue, sedentariness, low gait speed, muscle weakness) ; the second is that proposed by Mitnitski and Rockwood also in 2001, called the Frailty Index, aimed at identifying the number of "deficits" presented by the patient relative to the total deficits considered overall for the evaluation (in the original version, a total of 70 deficits were considered).
  It is now widely established that the relationship between polypharmacy and frailty is bidirectional: for example, the inappropriate use of certain medications (e.g., psychotropics, hypnotics, opioids, antihypertensives) increases the risk of falls; the presence of a depressive state (frequent in the elderly) induces prescription of additional drugs; prolonged polypharmacy is associated with cognitive decline and thus poor adherence. This spiral towards increasingly severe outcomes requires clinicians to use appropriate tools to identify and comprehensively assess frailty in old age (and hopefully also in the general population) in order to correctly estimate the risk-benefit index of each prescribed drug.
- Comorbidity. The presence of multiple diseases increases the rate of inappropriate prescriptions and drug-related problems. It is therefore necessary to correctly identify the main pathologies and the functional relationships they have both with other pathologies and with the response to administered pharmacological treatments. The use of a valuable tool like the Comprehensive Geriatric Assessment is essential, which must include rating scales such as the CIRS (Cumulative Illness Rating Scale), the Charlson Comorbidity Index (CCI), and the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II Scoring System [17-19]. This type of activity also allows characterization of any disability condition, defined as a state in which one or more physical and/or cognitive impairments affect the subject's ability to interact with the actual and social environment in which they are inserted; disability is strongly increasing and shows a marked correlation with comorbidity.
- "Cascade prescribing," i.e., the erroneous framing of a drug adverse effect as a new symptom to be treated with another drug. This issue concerns not only the physician, who instead of de-prescribing the drug responsible for the adverse effect adds another active ingredient to the therapy, but also the patient and the caregivers, who often use over-the-counter products to treat symptoms without prior clinical consultation. The correct identification of an adverse drug reaction requires non-trivial skills. However, in this delicate task the healthcare professional can be supported by tools such as the Naranjo Algorithm (a probability scale that involves assigning a score to a series of questions: the higher the sum of individual scores the higher the higher probability of experiencing an adverse reaction related to a given drug) or the WHO-UMC causality criteria, which classify ADRs as certain, probable, possible, unlikely, or indeterminate.
- Nutritional dysfunction. The risk of inadequate nutrition in the elderly is increased by numerous factors. Nutritional deficiency can cause alterations in the response to some drugs; for example, hypoalbuminemia in a patient taking phenytoin results in a lower fraction of the drug bound to albumin

(which acts as a carrier protein) and a higher free drug fraction in circulation. This in turn results in consequences such as confusional state and somnolence; the intake of herbal products (whose possible adverse effects are often underestimated) can determine interactions with drugs, as can alcohol intake (e.g., the synergistic effect produced by concurrent alcohol and benzodiazepines or barbiturates). On the other hand, some drugs can interfere with nutrient absorption, such as proton pump inhibitors that can cause iron malabsorption and consequent iron-deficiency anemia, or affect appetite levels, often conditioned by taste alterations. The nutritional status and eating habits of elderly patients should therefore be taken into consideration during the prescribing process, using appropriate rating scales.

The complexity of the prescribing process in the elderly requires the application of a Precision Prescribing strategy that provides the physician with unambiguous decision-making criteria. In addition to improving prescriptions with cross-cutting clinical value, such as medication reconciliation, de-prescribing, evaluation of drug-drug and drug-food interactions, and pharmacogenomics (see section 3.3), there are other important aids to pharmacological choice for prescribing in geriatric patients.
The Beers Criteria, developed by the American Geriatrics Society, provide a list of drugs classified as: potentially inappropriate in the elderly; potentially inappropriate in certain clinical conditions; to be used with caution; that cause potentially serious interactions in the elderly patient; that require dose reduction in patients with Chronic Kidney Disease.
The latest version of the STOPP/START Criteria (Screening Tool of Older Persons' prescriptions/Screening Tool to Alert doctors to Right Treatment) contain 114 recommendations to identify potentially inappropriate drugs (STOPP criteria) and drugs that are generally not prescribed in the elderly despite their appropriateness and absence of clear contraindications (START criteria). The application of the STOPP/START Criteria can have a significant impact on reducing healthcare costs.
The AEC Score (Anticholinergic effect on cognition score), which is useful for limiting the "anticholinergic burden" , stages a large number of active ingredients based on the clinical relevance of their anticholinergic effect with scores ranging from zero to three. If the sum of the scores of the drugs the patient is taking is greater than or equal to three, the patient's therapy should be reviewed in an attempt to reduce the burden of anticholinergic drugs.
Greater awareness of the value of such explicit criteria for appropriateness/inappropriateness of prescribing in the elderly would lead to a substantial increase in de-prescribing, which in clinical practice is often discouraged by therapeutic inertia and/or lack of appropriate timing in routine clinical practice. An explanatory example of the therapeutic potential of de-prescribing in the elderly is the chronic use of antipsychotics. In the case of patients with major neurocognitive disorders and BPSD (Behavior and Psychological Symptoms of Dementia), while the use of antipsychotics may be appropriate for symptom management in targeted cases and for limited periods of time, in continuous use, de-prescribing (particularly if implemented through slow tapering) is effective in 74% of patients, without a new increase in BPSD. Similarly, de-prescribing in the elderly should be considered in the frequent cases of chronic use of benzodiazepines or proton pump inhibitors, often used outside of recommendations.
Key recommendations for prescribing in elderly patients may include the following: critically review the therapy at every patient evaluation; ensure adequate monitoring of drugs that require it; start with low dosages and titrate slowly (the principle called "Start low, go slow"); avoid "automatically" prescribing a drug for every disease but consider the patient and their therapy holistically; check drug indications also through the STOPP/START criteria and other tools discussed; consider the possibility of de-prescribing; in case of onset of new symptom, consider the possibility that this may be due to the drugs taken and not to a pathological process; have adequate knowledge of the pharmacodynamics and pharmacokinetics of the active ingredients used; check that the patient does not take undeclared over-the-counter drugs, or herbal products or homeopathic preparations; verify that the patient has understood how to take the drug and is able to take it correctly; monitor the clinical response to prescribed drugs and any adverse effects over time.
It should not be forgotten that the use of any drug involves action on a repertoire of molecular receptors that are not always therapeutic targets. Therefore, recently a classification of Adverse Drug Reactions based on the on-target or off-target effects of the active ingredients has become more common, rather than a classification based on other characteristics of the active ingredients. For this reason, the possibility of accessing treatments that are as customized as possible to the patient's characteristics must be implemented, including pharmacogenomic studies for the correct identification of individual genetic factors predictive of drug response.
Table 2 lists some patient assessment tools and aids for prescriptive choice in geriatric patients.

Tabella 2. Some web resources for patient assessment and prescribing decision support

Web Resource	Description
https://www.omnicalculator.com/health/frailty-index	Allows online calculation of the Frailty Index according to Mitnitski. English language.
https://www.mdcalc.com/calc/10088/cumulative-illness-rating-scale-geriatric-cirs-g	Online calculation of the comorbidity index (CIRS). English language.
https://www.mdcalc.com/calc/3917/charlson-comorbidity-index-cci	Online calculation of the Charlson Comorbidity Index. English language.
https://www.farmacovigilanzasardegna.it/algoritmo-di-naranjo/	Online calculation of the Naranjo Algorithm for assessing the causal relationship between a drug and a suspected adverse reaction.
https://www.cgakit.com/_files/ugd/2a1cfa_bcf4d63c427e4e18963c64e74663728e.pdf	Download of a document listing the criteria. English language.
https://medstopper.com/	Allows classification from weak to strong of the recommendation for de-prescribing, by entering the patient's list of medications and pathology; if de-prescribing is recommended, gradual reduction methods are suggested; contraindications relative to the Beers Criteria are highlighted. English and French languages.
https://www.acbcalc.com/	Online calculation of the anticholinergic burden, by entering the complete list of medications taken by the patient. English language.

3. Tools for Improving Prescribing Appropriateness

3.1 Medication Reconciliation, Pharmacological Reconciliation, and De-prescribing

The increase in life expectancy and the progressive aging of the population are accompanied by an increase in the social and economic burden of chronic diseases and multimorbidity, leading to a constant increase in therapeutic regimens based on the administration of multiple drugs (polytherapy) and the associated risks, such as, for example, additive side effects, cross-interactions between drugs, and the multidisciplinary involvement in the therapeutic management of the patient by multiple healthcare professionals with growing coordination challenges among them. Combination therapy is associated with an increased risk of adverse events, especially during "Care Transition," that is the phase in which the patient moves between different hospital and/or community structures and home care. In such scenario, it is more likely that the different professionals taking care of the patient make changes or suspensions to the therapy.

Care transition is a critical moment in which the rate of prescribing discrepancies increases (Table 3) due to insufficient consultation and documentation of the patient's therapy, and in which therapy changes must be clearly understood by both the patient and their physician.]()

If carefully managed, this phase can however transform into an opportunity for therapeutic improvement, as it allows to verify, identify, and correct non-optimal therapies, through Pharmacological Reconciliation (PR) which may include de-prescribing of non-useful drugs, where appropriate.

The World Health Organization (WHO) and some international reference agencies (Joint Commission, Institute for Healthcare Improvement, etc.) recommend PR as one of the best strategies to ensure quality of care. In the WHO's "Action on patient safety: High 5s", it is included among the five priority strategies for pharmacological therapy. Therapeutic reconciliation represents a fundamental preparatory step for PR, aimed at collecting detailed and reliable information necessary to modify an ongoing therapy in an effective and safe manner. The topic was the subject of Ministry of Health Recommendation No. 17 of December 2014, addressed to public and accredited private acute and

post-acute hospital structures and residential and semi-residential outpatient public and private accredited health and social-health structures (community-based), as well as to general practitioners (GPs) /ambulatories and family pediatricians (FP), as well as to other care settings in which pharmacological therapy is prescribed and followed. The Recommendation provides for the use of a Reconciliation/Pharmacological Reconciliation (R/R) form, to be completed within 24 hours of patient intake, unless obstructing events occur that have to be appropriately recorded.

Table 3. Classification of Therapeutic Discrepancies According to "The High 5s Project", WHO.

Tipo	Descrizione	Esempio
Documented Intentional Discrepancies	These occur when the physician consciously decides to introduce, suspend, or modify a drug based on the new treatment plan, and this decision is clearly recorded in the clinical documentation.	A patient is admitted for a urinary tract infection and is prescribed an oral antibiotic that was not part of their home therapy. This variation is deliberate and recorded in the medical record. Similarly, if a physician suspends a supplement to avoid interactions with new drugs or because they deem it unnecessary for the patient, and then documents.
Undocumented Intentional Discrepancies	These occur when the physician makes a conscious decision regarding the patient's pharmacological therapy (introducing, suspending, or modifying a drug) but fails to report it in the clinical documentation. Although this discrepancy does not necessarily constitute an immediate therapeutic error, it can generate confusion and difficulties in patient management, especially during care transitions.	A patient on oral anticoagulants for a diagnosis of atrial fibrillation is admitted for surgery. The physician decides to temporarily suspend the anticoagulant but does not note down in the medical record how long before the surgery it was suspended nor s/he provides any indications regarding when to resume the drug. The lack of documentation could lead to misunderstandings in continuing the therapy.
Unintentional Discrepancies:	Involuntary errors in therapy management that can occur when a drug is omitted, added, or modified erroneously during care transitions.	
Omission	A drug that the patient was taking at home is not prescribed in the hospital by mistake.	Upon hospital admission, a thyroid supplement drug was erroneously added to the therapy because the patient, who was poorly cooperative and disoriented, brought the packages of all medications taken without specifying that the drug had been suspended two weeks earlier by the reference endocrinologist. During in-depth anamnesis collection with the aid of the patient's family, the physician proceeded to suspend the drug.
Commission	A drug that the patient was not habitually taking is erroneously introduced, with no clinical explanation or trace in the medical record.	Upon hospital admission, a thyroid supplement drug was erroneously added to the therapy because the patient, who was poorly cooperative and disoriented, brought the packages of all medications taken without specifying that the drug had been suspended two weeks earlier by the reference endocrinologist. During in-depth anamnesis collection with the aid of the patient's family, the physician proceeded to suspend the drug.

Some degree of flexibility is recognized to individual healthcare facilities and regional health authorities regarding the method of data collection (paper or electronic), content, and methods of communication, transfer, and storage of the form: "each healthcare facility shall develop a procedure that provides the necessary indications to complete the Pharmacological Reconciliation form, based on its own organization."

In any case, precise minimum requirements are specified:

- The reconciliation activity must include all prescription drugs as well as over-the-counter drugs without prescription obligation (SOP) and over-the-counter drugs, any investigational treatments and compassionate use drugs, with particular attention to collecting information related to the use of anticoagulants, antidiabetics, long-acting or prolonged-release medications, and immunosuppressive therapies; furthermore, it must include other products regularly taken such as supplements, herbal preparations, homeopathic remedies, and specific foods known for their pharmacological interactions.

- Data related to ongoing therapies must include:
    - Identification of the drug: trade name and/or active ingredient, pharmaceutical formulation, dosage, and daily posology (it is recommended to record exactly the data provided, without performing conversions between trade name and active ingredient or vice versa to avoid errors);
    - Details related to the therapy: start date, treatment duration, date and time of the last administration (with particular attention to long-acting drugs), route of administration (actual adherence to prescribed therapies and correct method of drug intake must be verified).
- Data related to relevant clinical and personal conditions must be collected: presence of diseases, allergies, intolerances, previous therapies and any adverse effects, anthropometric data (weight and height), medical devices in use or implantable, lifestyle-related risk factors such as alcohol consumption, illicit drug use, and smoking habit, and any other element deemed significant for the clinical-therapeutic management of the patient.

The accuracy of the data collected in the Reconciliation phase favors the subsequent pharmacological reconciliation process, which should be performed before proceeding with any prescription in order to avoid discrepancies or potential risks to the patient, according to the following phases and recommendations:

- Verification of drugs taken by the patient and their administration methods: any drug that has not been expressly prescribed or for which the need to continue or suspend it is not clearly indicated must be considered “unreconciled”, representing a potential risk of confusion, therapeutic error, and possible harm to the patient. Similarly, drugs for which it is not specified whether and how they have been modified in dosage or administration methods fall under unreconciled drugs.
- Assessment of the need for updates, modifications, or new prescriptions compared to the ongoing therapy.
- Verification of therapeutic consistency: comparison of the current therapy with the proposed therapeutic regimen, identifying possible inconsistencies, overlaps, duplications, omissions, or pharmacological interactions that could compromise efficacy or safety.

The reconciliation phase inherently holds enormous potential to intercept therapies at risk of inefficacy and toxicity, as well as to increase prescribing appropriateness in the pharmacological reconciliation phase. The efficiency and effectiveness of the reconciliation phase can be greatly increased in the near future, thanks to the growing availability of bioinformatics aids (Clinical Decision Support System - CDSS) and the development of artificial intelligence systems aimed not only at evaluating pharmacologically relevant drug interactions, but also at identifying prescription inconsistencies with respect to the set of relevant pharmacological indications and contraindications in relation to the patient's specific clinical and functional picture. Some available studies suggest that the use of systems capable of identifying therapeutic discrepancies, signaling pharmacological interactions, and supporting real-time clinical decision-making can not only improve the quality of therapeutic reconciliation and thus care, but also harmonize the execution of a critical activity like PR with healthcare workers' workflows. Bioinformatics and AI applied to the analysis of data collected in the reconciliation form will also allow identification of patients for whom pharmacogenomic testing or monitoring of plasma drug concentrations may be most appropriate and cost-effective, based both on the pharmacological characteristics of the medications taken and the patient's documented history of resistance or intolerance to treatments.

Systematic and coordinated actions must therefore be undertaken to extend and standardize reconciliation and pharmacological reconciliation practices in all care settings, overcoming current limitations.

To date, the practice of reconciliation and pharmacological reconciliation is most commonly implemented in hospital facilities, with transfer of the R/R form to the Clinical Record. It would instead be appropriate to incentivize and monitor reconciliation and pharmacological reconciliation activity at all public and private care points, making healthcare workers aware of the benefits provided and risks avoided. This can be achieved by transforming recommendations into

regulations that explicitly mandate the activity in certain cases (e.g., patients over 65, psychiatric patients, etc.), while addressing organizational aspects to facilitate the activity for operators. The continuity and consistency of R/R documentation across different care settings should be ensured through the use of a single digital form, which can be easily consulted and updated, to track all therapeutic transitions that have occurred in the patient's clinical history, accompanied by indications of the methods and reasons why they occurred. The usability of the R/R form is limited by the way in which it is shared and communicated (both to the patient and the physician in charge): the fragmentation of care and the difficulties in coordination between specialists and GPs represent significant obstacles. A uniform method of data transfer (e.g., converging on the Electronic Health Record) would implement an information flow that connects all nodes of the care network: hospital (wards and outpatient clinics) - community physician (GP, Pediatrician, specialist, health homes...) - residential facility - patient.

It is also worth remembering that workload and limited time increase resistance to change among involved healthcare personnel, partly due to the perception of increased work complexity. This barrier can be overcome by promoting a culture of patient communication as a means of streamlining the care process: it is important to approach therapeutic reconciliation and pharmacological reconciliation as a form of professional investment, which, in exchange for an initial investment of time and resources, will return an improvement in care quality that reasonably translates into a net gain of such resources. Furthermore, physicians must be familiarized with the potential and limitations of the various algorithms currently available to support the reconciliation phase (including drug-drug interaction assessment), and provided with the necessary skills to cope with the massive entry of bioinformatics and AI systems into diagnostic and care processes.

Among the expected benefits of systematic therapeutic reconciliation and pharmacological reconciliation activity, a strong incentive for de-prescribing is anticipated (i.e., the reduction or suspension of drugs that are no longer necessary, appropriate, or that carry a risk greater than the expected benefits).

This practice is particularly relevant in elderly patients and those with chronic diseases managed in internal medicine wards and outpatient clinics, polypharmacy-treated or with multimorbidity, to reduce the risk of adverse reactions, pharmacological interactions, and iatrogenic events. According to Scott et al., Pharmacological De-prescribing is a "planned and supervised process of dose reduction or drug discontinuation, conducted to improve patient outcomes and reduce adverse drug events" and therefore represents a structured clinical process aimed at critically reviewing the ongoing pharmacological therapy. The broad impact of this practice on public health and optimization of healthcare resources is a well-described and accepted concept, to the extent that several national programs have been undertaken to promote its dissemination. The Canadian Deprescribing Network (CaDeN) has developed evidence-based guidelines for discontinuing high-risk drugs such as proton pump inhibitors (PPIs), benzodiazepines, antipsychotics, and oral hypoglycemics. The Australian National Prescribing Service (NPS MedicineWise) promotes de-prescribing strategies through educational programs targeted at physicians and pharmacists with the contribution of pharmacologists; the NHS Polypharmacy Action Plan in the United Kingdom provides for regular therapy review in patients with multimorbidity, with the aim of reducing inappropriate prescribing.

In Italy, the National Outcomes Program (PNE) of the National Agency for Regional Health Services (AGENAS) includes de-prescribing among strategies to improve therapeutic safety in chronic patients. Furthermore, inter-society guidelines have been issued for managing polypharmacy in the elderly, with a focus on reducing inappropriate drugs. The methodical and individualized approach identified for controlled and effective de-prescribing well illustrates the steps of reconciliation, articulated in the following phases:

1. Identification of Potentially Inappropriate Medications (PIMs):

- Assessment of therapeutic need in relation to the patient's clinical condition
- Analysis of risk-benefit ratio based on scientific evidence
- Use of validated tools for identifying inappropriate drugs, including: Beers Criteria (American Geriatrics Society); STOPP/START criteria (Screening Tool of Older Persons' Prescriptions); MedStopper (interactive decision-making tool for de-prescribing).

2. Planning of reduction or discontinuation:

- Immediate suspension for drugs with a high-risk profile or lack of benefit (e.g., benzodiazepines in the elderly)
- Gradual reduction for drugs with potential risk of withdrawal syndrome or rebound effect (e.g., beta-blockers, antidepressants, opioids).

3. Monitoring and follow-up:

- Clinical evaluation of the patient after discontinuation
- Detection of any withdrawal symptoms or worsening of the underlying disease
- Possible reintroduction of the drug if necessary.

Several national studies have demonstrated the effectiveness of the de-prescribing approach, but wider application of the practice is evidently contingent on the adoption of precise and shared guidelines by both administrators and medical associations/federations.

3.2 Software for Pharmacological Interaction Analysis

The preventive analysis of potential Drug-Drug Interactions (DDIs) using bioinformatics tools (CDSS, databases, commercial and non-commercial web applications) is increasingly important, given its enormous potential to guide the selection of combination therapies while minimizing harmful interactions. Furthermore, the widespread accessibility of CDSS for physicians and patients has made the topic of DDIs "popular," raising public awareness of the importance of their prevention, but also posing the risk of oversimplification and thus improper interpretation of the clinical significance of DDIs.

It is worth noting that a meta-analysis of studies conducted in hospitalized patients revealed a substantial gap between the number of potential DDIs predicted by software or algorithm-based tools and the actual prevalence of DDIs that resulted in observable clinical effects. This highlights the need to validate and certify the tools used for such analysis, as well as to refine the parameters used to classify predicted DDIs according to their actual risk of clinical manifestation. Additionally, prescribers must be trained to better understand the mechanisms underlying the onset of a drug-drug interaction, since - regardless of the use of DDI analysis tools- the physician remains the key decision-maker, responsible for performing a comprehensive risk-benefit assessment for each patient.

Numerous freely accessible "drug interaction checkers" are available online (Table 4), and several also offer corresponding smartphone applications, Most provide information on the mechanism of interaction and the potential clinical consequences, generally classifying the interaction as mild, moderate, or severe. Often, these applications also allow queries on possible drug-food interactions or interactions with other substances, such as herbal products or supplements. Some tools, such as INTERcheck- developed by the Mario Negri Institute for Pharmacological Research IRCCS- offer more sophisticated clinical decision support. In addition to interaction analysis, these systems provide a broader assessment of prescribing appropriateness, indicating, for example:

- Potentially inappropriate drugs in older adults (Beers Criteria; START/STOPP; STOPP Frail);
- Anticholinergic burden;
- Methods for discontinuing drugs requiring gradual dose reduction;
- Dosing in subjects with impaired renal function;
- Choosing Wisely-Italy recommendations on pharmacological therapy;
- Risk/benefit assessment via NNT (number needed to treat for a beneficial outcome) and NNH (number needed to harm for an adverse effect);
- Compatibility assessment for drugs administered in vials;
- GerontoNet ADR Risk Score calculation, aimed at identifying patients at higher risk of adverse reactions;
- Assessment of causality between a drug and an adverse event via the Naranjo algorithm;
- Assessment of causality between adverse event and drug interaction via the DIPS algorithm (Drug Interaction Probability Scale).

Some drug interaction checkers are dedicated to specialist areas, such as the "Cancer drug interaction checker" developed by the University of Liverpool, which allows evaluation of the compatibility between chemotherapeutics and other drugs required by the patient. The same university provides the "HIV drug interactions," "HEP drug interactions" (for anti-hepatitis drugs), and developed during the pandemic the "COVID-19 drug interactions" (Table 4).

Alongside these freely consultable tools, a wide range of commercial software has also been developed. This increasingly broad availability has encouraged studies aimed at using these systems to estimate DDI prevalence in various clinical settings, and to evaluate the utility of systematising DDI assessment. The results clearly highlight the efficiency of these tools in quickly identifying potential pharmacological problems [45-49], but, as already mentioned, they also bring to light several issues that must be considered to ensure conscious interpretation and appropriate use of the information obtained.

The most important of these is undoubtedly system accuracy: it should be remembered that these IT tools are not always clinically validated across the entire process of (i) DDI assessment, (ii) therapeutic decision-making, and (iii) patient follow-up. They tend to overestimate the frequency and/or severity of pharmacological interactions and rarely provide a strategy for mitigating the risk of clinically significant DDIs. Furthermore, it is not always fully known or disclosed which sources of information the different systems draw upon for DDI assessment (e.g. summary of product characteristics, case reports, preclinical studies, clinical evaluations with or without dechallenge and rechallenge of the suspected DDI drug), which represents a serious concern regarding the quality of the support data provided to the physician. It is also worth emphasizing that these IT tools usually do not typically integrate, concurrently or comprehensively, the assessment of parameters influencing DDI manifestation, such as pharmacokinetic covariates, indices of organ excretion function, the net effect of concurrent drug-metabolism inducers and inhibitors, the therapeutic index of drugs, and the inevitability of certain interactions (e.g., patient stabilized on background therapy who must modify therapy due to a DDI that may have no clinical relevance, with the consequent -potentially severe- risk of "end-of-treatment" adverse reactions that are not justified by the DDI risk).

Several studies have shown that the performance of different prediction and severity-assessment systems varies depending on the databases used (completeness of information) and on the algorithms applied (i.e. the weight assigned to different information) [50-54]. Discrepancies in assessment can result in diametrically opposite effects in prescribing practices, either underestimating or overestimating the risk associated with a given therapy. Overestimation can be particularly harmful, generating inconsistent alerts and prompting therapy modifications that may adversely affect therapeutic benefit. Even the recommendations provided on how to manage interactions are not always consistent across systems.

In conclusion, it is certainly desirable for the scientific community to establish a more uniform method for cataloguing, assessing, and managing pharmacological interactions.

In the meantime, the limitations described can be mitigated, first and foremost through an informed selection of the software to be used, i.e., by documenting (i) the data sources employed and assessing their authority, and (ii) the availability of scientific literature describing their limitations and potential, ideally within one's own clinical area of interest. Furthermore, indiscriminate use of CDSS for DDI analysis is not advisable; rather, their use should be limited to situations where therapeutic risk is objectively high, and in all cases reference should be made to expert pharmacological assessment through consultation.

It is reasonable to expect that these predictive systems will evolve rapidly, supported by the training of artificial intelligence models, to incorporate additional essential functionalities for improving polytherapy management, such as:

- Prediction of effects produced by networks of drug interactions (multi-drug approach): most current analysis algorithms evaluate potential interactions between two drugs at a time. The net effect of multiple interactions could differ substantially from what is predicted based solely on pairwise interactions.
- Integration of DDI assessment with other predictive factors of drug response, including recommendations for drug use in specific patient categories or in the presence of pharmacogenomic variants.
- Guidance for replacing potentially inappropriate drugs identified with alternative medications more compatible with co-administered medicines and with the patient's overall clinical profile.

Despite the limitations described above, the enormous potential of disseminating and correctly applying DDI analysis should not be overlooked. The universal accessibility and affordability of many DDI analysis tools make it possible to translate a Precision Medicine approach directly into real life (without social, economic, or territorial disparities), enabling general practitioners to identify a significant proportion of frail and multimorbid patients whose therapy could be improved.

At present, however, to ensure appropriate use of these tools, access to pharmacological consultation by experts in the field - who assume responsibility for the assessment - must be considered. It is also essential to promote rigorous projects aimed at the clinical validation of CDSS, so that large-scale measurement can then be conducted on changes induced in prescribing practices, treatment efficacy and safety, and the use of pharmaceutical resources. This validation must occur with the support of the DDI expert professional, considering that discrepancies between software-generated assessments and those of expert pharmacologists frequently emerge.

Table 4. Non exhaustive list of free web resources for the assessment of pharmacological interactions

Name	link
INTERCheck	https://intercheckweb.marionegri.it
Medscape Drug Interaction Checker	https://reference.medscape.com/drug-interactionchecker
Drugbank	https://go.drugbank.com/drug-interaction-checker
Drugs.com	https://www.drugs.com/drug_interactions.html
WebMD	https://www.webmd.com/interaction-checker/default.htm
CANCER-druginteractions	https://cancer-druginteractions.org/checker
HIV-druginteractions	https://www.hiv-druginteractions.org/
HEP-druginteractions	https://www.hep-druginteractions.org/checker#
COVID19-druginteractions	https://covid19-druginteractions.org/
DDInter	http://ddinter.scbdd.com/

3.3 Pharmacogenetics and Pharmacogenomics

The term *pharmacogenetics* refers to the prediction of an individual's response to drug administration based on the presence of one or more genetic markers, i.e., sequence variations in DNA. Such variations determine qualitative or quantitative alterations in gene products (proteins) involved in pharmacodynamics (drug receptors) or pharmacokinetics (drug metabolizing enzymes and drug transporters), which can result in reduced or absent efficacy or increased toxicity of the administered active ingredient.

It is therefore clear that characterizing a pharmacogenetic marker increases the predictability of a drug's efficacy and tolerability, and becomes a factor capable of improving prescribing appropriateness according to the specific characteristics of each patient, fully realizing the founding principles of Precision Medicine. However, the predictive power (and thus the clinical utility) of genetic markers of drug response is highly variable. For a publicly funded healthcare system, this variability implies the need to identify clinical settings and modes of use that best ensure the sustainable delivery of such tests.

The DNA variations (markers) studied in pharmacogenetics occur at a higher frequency in the population (greater than 1%) compared with rare mutations, because the functional alteration they induce does not cause a particularly severe clinical phenotype (and is therefore not associated with to genetic diseases) and in fact produces no manifest phenotype unless the organism is exposed to the drug. Structurally, these variants consist mostly of single nucleotide polymorphisms (SNPs), but may also include insertions or deletions of one or a few nucleotides; VNTRs (variable number tandem repeats), involving a variable number of copies of a short repeated DNA sequence; or deletions or duplications of an entire gene. Moreover, some so called "pharmacogenes" are highly polymorphic, meaning that dozens—or even

hundreds—of different alleles characterized by multiple polymorphisms exist within the population. In such cases (with cytochrome CYP2D6 being the prime example), the functional consequence of the allelic combination detected in a patient is reported clinically as a predicted "phenotype" (derived from genotype-to-phenotype conversion), usually expressed as normal, poor, rapid, or ultrarapid metabolizer, according to the increased or decreased metabolic activity of the enzyme in question.

Whereas at the dawn of pharmacogenetics, technological and financial constraints (high analytical cost) restricted tests to a few high impact markers - typically in oncology- the spread of increasingly powerful and relatively low cost analytical methods (especially next generation sequencing, NGS) now allows hundreds of drug response genetic markers to be characterized in a single analytical session. This shift enables the transition from pharmacogenetics to "pharmacogenomics," even though the terms are often used interchangeably (from this point onward, the acronym PG will be used to denote both, derived from *Pharmaco Genetics/Genomics*). However, while technological advances and the development of bioinformatic systems for interpreting large volumes of complex data have progressed rapidly, healthcare systems have not advanced at the same pace in planning, regulating, and uniformly delivering the clinical and diagnostic services needed to ensure appropriate PG use.

A clear overview of the current situation emerged from the "Multi stakeholder workshop on Pharmacogenomics" held in September 2024 and organized by the European Commission, the European Medicines Agency (EMA), and the Heads of Medicines Agencies (HMA). The workshop report highlights the heterogeneity of pharmacogenomics implementation approaches, comparing experiences from Belgium, Germany, the United Kingdom, and Spain, and emphasizing that a major challenge is the lack of alignment in recommendations and guidelines for the use of pharmacogenomic markers issued by leading scientific consortia such as CPIC (Clinical Pharmacogenomics Implementation Consortium) and DPWG (Dutch Pharmacogenetics Working Group), as well as by regulatory agencies such as the FDA and EMA. These discrepancies are largely attributable to inconsistent evidence regarding the effectiveness of certain pharmacogenetic tests, mainly due to the diversity of clinical settings and outcomes examined in available studies.

Among the main organizational limitations identified - common across national PG test implementation efforts, are:

- Incomplete pharmacogenetic/pharmacogenomic information in the Summary of Product Characteristics (SmPC) and in the Package Leaflet (PL) accompanying medicines;
- Absence of standardized and interoperable methods for recording and using genomic data, which also prevents broad and systematic data collection capable of generating evidence on the cost-benefit profile of specific diagnostic-clinical strategies that include pharmacogenomics;
- Insufficient information and training regarding the appropriate use of pharmacogenomic tests in clinical practice.

To these issues must be added the lack of standardization in reporting methodology, which can lead to misinterpretation by physicians (as discussed later).

More recently, the potential, feasibility, and sustainability of PG in Italy have been examined by a multidisciplinary working group of the Università Cattolica del Sacro Cuore as part of the European project PROPHET (A PeRsOnalized Prevention roadmap for the future HEalThcare, prophetproject.eu). The overarching goal of PROPHET is to develop a strategic roadmap for implementing personalized prevention in Europe, leveraging genomics and other technologies to improve health outcomes. Within this project, a set of recommendations has been developed to support the sustainable adoption of preventive PG strategies in Italy, following a multi stage approach based on review of available literature, analysis of public data, and iterative consultations with a multidisciplinary Steering Committee composed of clinicians and researchers with expertise in the field. The working group identified four interconnected dimensions as cornerstones for implementing PG panels within the NHS: clinical utility, economic sustainability, patient acceptability, and organizational feasibility, as described below.

Clinical utility. Several organizations, including the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Dutch Pharmacogenetics Working Group (DPWG), and the French National Pharmacogenetics Network (RNPGx), have played a central role in developing evidence-based PG guidelines, mostly based on pharmacokinetic studies and implementation data, given the scarcity of randomized clinical trials. A recent

review of randomized clinical trials and real-world studies conducted in the United States and Europe by Chenchula et al. generally supports the clinical utility of PG. One of the largest randomized trials is the PREPARE study, which assessed the utility of a panel comprising 50 variants in 12 genes, involving 6,944 patients in seven European countries, including Italy. The results suggest that a therapeutic approach guided by PG information may help reduce adverse drug reactions, hospitalizations, emergency department visits, and healthcare costs. However, some authors have criticized the study design, highlighting the complexity of defining and controlling all possible confounding factors in an evaluation study of PG tests.

Economic sustainability. The economic sustainability of PG reflects its clinical utility; therefore, a rigorous cost analysis can only be performed after establishing the clinical domains of appropriateness (i.e., utility) of specific PG tests. This is illustrated by several examples of cost-effectiveness studies of monogenic tests: a systematic review of 47 economic evaluations provided strong support for the cost-effectiveness of HLA-B*57:01 testing for abacavir hypersensitivity and CYP2C19 testing for clopidogrel therapy, whereas results for markers such as TPMT and CYP2C9 were discordant. Another review, including 80 evaluations, found that most PG-guided therapies were cost-effective or even cost-saving, although results varied depending on factors such as biomarker prevalence, test cost, ADR incidence, and therapy response rates. Similarly, a review by Morris et al., covering 108 studies and 39 drugs, concluded that 71% of PG tests were cost-effective or cost-saving - particularly for clopidogrel, warfarin, and antidepressants - while noting the lack of data on multigene panels, which are increasingly replacing monogenic tests due to comparable analytical costs achieved through technological advances [72–74]. Among the limited data available on multigene PG panels, cost-utility assessments conducted within the U-PGx project and based on Italian patients with colorectal cancer included in the PREPARE trial [5–78] showed lower costs per patient in the PG-guided therapy arm (€380 vs €565). Subgroup analyses further indicated that, in patients carrying actionable variants, PG-guided therapy represented a dominant strategy, with a 92% probability of being cost-effective.

Patient acceptability. Patient understanding and adherence are essential conditions for the effective implementation of PG testing in clinical practice; however, studies exploring patient perspectives in Italy and Europe remain limited. A large survey conducted in the United Kingdom estimated that acceptance of PG testing could range between 51% and over 99%, depending on how the service is structured - particularly regarding test invasiveness, the mode of accessing results, and regional data-sharing practices. Similarly, studies in the United States and Canada indicate that most patients express a favorable attitude toward PG testing, provided they receive adequate information, and support its use to guide clinical decisions [81–84]. The PREPARE trial further reinforced this evidence, demonstrating the feasibility of large-scale PG implementation across Europe.
Despite this, significant barriers remain. Several studies have identified low patient awareness, concerns about genetic privacy, fear of inappropriate use of data, and the risk of insurance discrimination as major obstacles [85–87]. These concerns often appear even more pronounced among vulnerable populations or minority groups. In addition, pilot studies suggest that - even when PG tests are offered free of charge- uptake rates can remain low in the absence of adequate understanding or personalized informational support.

Organizational feasibility. Several organizational barriers currently limit the integration of PG tests within the Italian NHS. One of the main challenges is the absence of clear and uniform reimbursement strategies, resulting in heterogeneous implementation across Regions.
Infrastructure disparities further exacerbate inequalities in access to PG services. According to AGENAS data, laboratories authorized to perform PG tests are concentrated primarily in Northern Italy, with Lombardy alone hosting 28 facilities. In contrast, Southern Regions and the Islands are severely under-equipped, with only two structures in Sardinia. Overall, 67 facilities are located in the North, 24 in the Centre, 23 in the South, and 17 in the Islands. This uneven distribution contributes to regional inequalities and hampers the potential for nationwide implementation.
Technical issues also persist. Many healthcare facilities lack adequate systems for managing, interpreting, and sharing pharmacogenetic data. Integration of genetic results into clinical workflows and electronic health records is hindered by the absence of standardized infrastructures. Significant challenges remain in developing clinical decision support tools (CDS), in consistently translating genotype to phenotype, and in ensuring

interoperability across institutions. These problems were also highlighted by the U-PGx project, which evidenced both technical and institutional complexities associated with large-scale PG implementation [64, 92–94]. Added to this are training gaps among healthcare personnel, which continue to represent a major barrier. Although many clinicians recognize the value of PG testing, confidence in selecting, interpreting, and applying results remains low, partly due to the lack of targeted training opportunities [93–97]. A survey conducted in Southern Italy showed that only a minority of physicians and residents feel adequately prepared for the clinical use of PGx tests, despite a high level of interest and awareness of their potential.

Thus, to understand the true state of the art of PG and to identify the most effective way to support its uniform, clinically useful, cost-effective, and widely acceptable application for both patients and prescribers, a few preliminary considerations are necessary.

First, it is necessary to distinguish PG tests performed on somatic cells from those performed on germ cells. These two branches should be treated separately from both regulatory and organizational standpoints. It is no coincidence that most existing recommendations on PG testing concern the administration of oncology drugs, with specific indications for use depending on the presence or absence of somatic mutations. In this context, the framework of test-prescribing appropriateness and the guidelines for adapting treatment are well established and have strongly encouraged the development of targeted therapies that take into account the specific somatic characteristics of the tumor. By contrast, for PG tests on germline DNA, the state of the art is far more heterogeneous. In oncology, once again, the landscape of clinically useful tests is relatively well defined, whereas this is not the case in other clinical areas, where it has been - and remains - more difficult to complete cost-effectiveness and cost-benefit studies.

Second, a significant gap has emerged between PG tests delivered within the LEAs of the Italian NHS and the analytical and applicative possibilities of PG as a discipline. While the SSN offering is essentially based on single gene-drug pairs, the reality of pharmacogenomic science has rapidly shifted toward a multigene, multidrug approach in which many variants are analyzed to produce informative data relevant to a large number of drugs. Foresight - indispensable for healthcare stakeholders- requires acknowledging that the result of germline DNA analysis (partial or whole) has the fundamental characteristic of immutability. It can therefore be obtained once in a patient's lifetime, yet potentially be used throughout all pharmacological treatment situations encountered over the course of that patient's life.

Third, the private sector's provision of multigene tests is expanding exponentially, meaning that health authorities cannot ignore, beyond SSN-delivered tests, the need to plan a governance strategy for PG data management, both in terms of acquisition and use. We are in a transitional phase that will soon see the widespread availability of rapid and relatively inexpensive whole-genome sequencing for every patient. Moreover, AI will be extensively applied to personalized drug prescribing, generating further organizational and regulatory needs.

3.3.1 Germline PG testing offer in Italy

The DPCM of 12 January 2017 defined the LEA, fully replacing the DPCM of 29 November 2001. Annex 4 to the DPCM contains the updated nomenclature for outpatient specialist care; the related tariffs are set out in the Ministry of Health decree of 25 November 2024 (version with annexes), issued jointly with the Ministry of Economy and Finance (MEF) and published in the Gazzetta Ufficiale on 27 December 2024. The codes for PG tests present in the nomenclature are:

- G3.01 – Detection of known mutations/known polymorphisms. Pharmacogenetics of drug-metabolizing genes: CYP2D6 (prescribable with note 94: Only for gefitinib, according to EMA recommendations).
- G3.02 – Detection of known mutations/known polymorphisms. Pharmacogenetics of drug-metabolizing genes: CYP2C19 (prescribable with note 95: Only for atazanavir, according to EMA recommendations).
- G3.03 – Detection of known mutations/known polymorphisms. PHARMACOGENETICS IN ONCOLOGY: UGT1A1 (prescribable with note 96: Only for erlotinib, according to EMA recommendations).

Compared with this offer, it should be noted that additional recommendations for pharmacogenomic testing have been issued by various regulatory agencies, some based on clinical evidence comparable to -or stronger than- that available for atazanavir. For example, for mavacamten, the EMA recommends the CYP2C19 test (G3.02); for irinotecan, AIFA recommends the UGT1A1 test (G3.03). Moreover, AIFA considers PG tests for the HLA B gene mandatory to avoid serious adverse reactions to abacavir, and for the DPYD gene to prevent severe toxicity related to fluoropyrimidines. Only by using code G1.01_0 (Mutational analysis of a disease requiring a single gene for diagnosis. Sequencing and, where applicable, quantitative method, any technique) is it possible to request characterization of the DPYD gene, which is associated with the genetic disease P282 (dihydropyrimidine dehydrogenase deficiency).

Below is a description of a limited number of pharmacogenomic markers whose clinical utility is widely recognized by the scientific community (when used in appropriate patient categories), and whose inclusion in the LEA should be considered. Clinical recommendations developed by the main scientific consortia (Clinical Pharmacogenetics Implementation Consortium, Dutch Pharmacogenetics Working Group, DPWG) can be consulted on the comprehensive web platform ClinPGx (https://cpicpgx.org/).

PG markers in oncology

- DIHYDROPYRIMIDINE DEHYDROGENASE AND FLUOROPYRIMIDINES. Fluoropyrimidines (5 FU, capecitabine, tegafur) can cause severe gastrointestinal and hematological toxicities primarily due to impaired clearance. The main enzyme responsible for their catabolism is dihydropyrimidine dehydrogenase (DPD), encoded by the DPYD gene, which carries allelic variants associated with reduced enzymatic activity. To prevent potentially very severe adverse reactions, the EMA Pharmacovigilance Risk Assessment Committee, in its note of 13/3/2020 (EMA/125891/2020), recommends performing the DPYD test in all patients considered candidates for fluoropyrimidine treatment. As a consequence of this position of the European regulatory agency—arising from extensive toxicogenomic and epidemiological work conducted in Italy and other European countries —a working group was established between the Associazione Italiana di Oncologia Medica (AIOM) and the Società Italiana di Farmacologia (SIF), which drafted national recommendations. Based on functional and epidemiological evidence, analysis of the following variants is recommended: c.1236G>A (c.1129–5923C>G), c.1679T>G, c.1905+1G>A, and c.2846A>T. Based on literature data, in the presence of good treatment tolerance, dose titration is suggested when the c.1236GA/AA variant is detected. In the presence of c.1679GG, c.1905+1AA, and c.2846TT in homozygosity, administration of fluoropyrimidines is not recommended. If the variants c.1679TG, c.1905+1GA, and c.2846AT are detected in heterozygosity, the recommended fluoropyrimidine dose is 50%. Finally, if c.1236AG or c.1236AA are present, the suggested starting fluoropyrimidine doses are 75% or 50%, respectively. In both cases, however, treatment should be titrated up to 100% based on patient tolerability.
When toxicity persists after treatment initiation, assessment of additional variants (e.g., c.2194G>A) may be useful. In this case, in the presence of c.2194GA (heterozygous) or c.2194AA (homozygous), drug doses should be 80% and 70%, respectively.

- UGT1A1 AND IRINOTECAN. Irinotecan can cause severe gastrointestinal and hematological toxicities mainly attributable to impaired clearance. The key enzyme responsible for irinotecan catabolism is uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), which conjugates the active metabolite SN 38 with glucuronic acid. The UGT1A1 gene is highly polymorphic and can determine variable metabolic capacity among individuals. The best characterized UGT1A1 genetic variants are UGT1A1*28 and UGT1A1*6. These variants and other congenital defects in UGT1A1 expression are associated with reduced expression and activity of this enzyme. To prevent potentially severe adverse reactions, UGT1A1 pharmacogenetic analysis is recommended: a) before irinotecan therapy whenever, in the oncologist's judgment, treatment is proposed to a patient whose clinical characteristics (comorbidities, performance status, disease stage) suggest limited impact on survival and/or response and/or a high risk benefit ratio; b) during irinotecan therapy in cases of grade ≥3 gastrointestinal toxicity and/or grade 4 hematological toxicity (NCI CTCAE v.4.0), and in all cases of unexpected severe toxicity.

In the presence of *28/*28 or *6/*6 in homozygosity, the recommended irinotecan dose is 70%; with the same variants *1/*28 or *1/*6 in heterozygosity, the irinotecan dose administered should be 100%.

- TPMT, NUDT15 AND THIOPURINES. Mercaptopurine is an immunosuppressive and antineoplastic agent belonging to the class of thiopurines. It is used in combination with other drugs for the treatment of acute lymphoblastic leukemia. Among the most common off label uses is the treatment of inflammatory bowel diseases (IBD). Mercaptopurine is a prodrug that must first be activated to form thioguanine nucleotides (TGN), of which 6 thioguanine triphosphate (6 TGTP) is the main active metabolite. Two of the enzymes involved in the complex metabolic pathway of these metabolites are thiopurine S methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15). Subjects with reduced activity of one of these two enzymes are exposed to higher levels of active metabolites, such as 6 TGTP, and are at greater risk of side effects, including severe myelosuppression. The FDA approved technical sheet of the drug states that the starting dose of mercaptopurine must be reduced in subjects carrying homozygous loss of function variants of TPMT or NUDT15, and that these subjects usually require a dose equal to or lower than 10% of the standard dose. In subjects with reduced enzymatic activity (heterozygous condition), the technical sheet states that the mercaptopurine dose must be reduced according to tolerability. A more substantial dose reduction may be necessary in subjects with reduced activity of both enzymes. The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) have also published dosing recommendations for mercaptopurine based on TPMT and NUDT15 genotype. These recommendations include specific dose reductions for individuals with low or deficient enzymatic activity, including the starting dose and further guidance on how and when to adjust the dose, for example, the time allowed to reach steady state after each dose adjustment.

PG markers in neurology

- CYP2C9 AND SIPONIMOD. Siponimod is a functional antagonist of sphingosine 1 phosphate receptors (S1PR) subtypes 1 and 5 and is metabolized mainly by CYP2C9 and, to a lesser extent, by CYP3A4. The CYP2C9 gene is polymorphic, and activity scores assigned to each allele are used to categorize the phenotype. Reduced CYP2C9 metabolic activity is associated with an increased risk of adverse effects after exposure to siponimod. Therefore, siponimod use is contraindicated in subjects with the CYP2C9*3/*3 diplotype (activity score = 0). In subjects carrying one non functional *3 allele (diplotypes with activity scores of 0.5 or 1.0), it is recommended to take half the standard maintenance dose. Consideration of genotype and activity score is essential for CYP2C9 based siponimod dosing, since the posology recommendations reported in the label are not categorized by phenotype. European prescribing guidelines do not modify the titration schedule for individuals with a single CYP2C9*3 allele (CYP2C9*3 heterozygotes). The Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy similarly recommends a 50% reduced maintenance dose for intermediate metabolizers (IM). It should be noted that the dosing recommendations in the siponimod technical sheet are limited to diplotypes composed only of CYP2C9 *1, *2, and *3 alleles due to the lack of clinical data on the impact of other reduced or non functional alleles, whereas other guidelines for drugs and tests also consider *5, *6, *8, and *11. According to EMA, the standard dose is recommended for subjects who do not carry a CYP2C9*2 or *3 allele, while a reduced maintenance dose of 1 mg is recommended for subjects with genotype CYP2C9*1/*3 or *2/*3. Siponimod is contraindicated in *3/*3 homozygotes. Theoretically, the risk of adverse effects is markedly increased, as the genetic variation leads to much higher plasma concentrations of siponimod.

PG markers in infectious diseases

- CYP2C19 AND VORICONAZOLE. Therapeutic drug monitoring of voriconazole has become the standard of care to ensure efficacy and avoid adverse effects. Low serum voriconazole concentrations have been associated with treatment failure, which can have devastating consequences in severely ill patients with invasive infection. High serum voriconazole concentrations are associated with adverse effects, such as neurotoxicity. Interindividual serum drug concentrations vary widely among subjects treated with the same voriconazole dose, partly due to genetic variation in the CYP2C19 gene. Voriconazole is metabolized mainly by the enzyme CYP2C19, with contributions from CYP2C9 and CYP3A4. Subjects with low CYP2C19 activity ("CYP2C19 poor metabolizers") have, on average, 4-fold higher voriconazole exposure than normal metabolizers. Conversely, individuals with increased CYP2C19 activity ("rapid" and "ultrarapid metabolizers") have lower serum voriconazole concentrations. Genetic tests for voriconazole response and for the CYP2C19 gene are currently available. Dosing recommendations for voriconazole based

on CYP2C19 metabolizer subtype are available from the Dutch Pharmacogenetics Working Group (DPWG) and the Clinical Pharmacogenetics Implementation Consortium (CPIC).

- UGT1A1 AND ATAZANAVIR. Atazanavir is a protease inhibitor antiretroviral (PI) used to treat HIV infection in adults and children and is part of a multi-drug regimen. Although it was once widely recommended as first-line therapy, it is now mainly suggested as a second-line therapeutic option due to potential adverse effects leading to treatment discontinuation. Atazanavir can cause hyperbilirubinemia (not associated with liver damage) resulting in jaundice, which is a common cause of drug discontinuation. Individuals with two reduced-function alleles for UGT1A1 are more likely to develop jaundice leading to atazanavir discontinuation, although this may occur even in individuals with a genotype associated with normal UGT1A1 function. The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends that, when an individual is known to be a UGT1A1 poor metabolizer, an alternative therapy should be considered, especially when jaundice is a concern for the individual. The technical sheet of the drug approved by the U.S. Food and Drug Administration (FDA) states that some concomitant therapies that depend on UGT1A1 or the cytochrome P450 family member CYP3A are contraindications to atazanavir therapy due to the potential increase in plasma concentrations of these concomitant therapies.

PG markers in cardiology

- CYP2C19 AND CLOPIDOGREL. Clopidogrel is an antiplatelet drug that reduces the risk of myocardial infarction (MI) and stroke in subjects with acute coronary syndrome (ACS) and in those with atherosclerotic vascular disease (indicated by recent MI or stroke, or confirmed peripheral artery disease). Clopidogrel is also indicated in combination with aspirin in subjects undergoing percutaneous coronary interventions (PCI), including stent placement. The efficacy of clopidogrel depends on its conversion into an active metabolite, which is carried out by the cytochrome P450 enzyme CYP2C19. Subjects who carry two loss-of-function copies of the CYP2C19 gene are classified as CYP2C19 poor metabolizers (PM). Individuals with a CYP2C19 PM phenotype have significantly reduced enzymatic activity and cannot activate clopidogrel via CYP2C19, meaning the drug will have reduced antiplatelet effect. Approximately 2% of Caucasians, 4% of African Americans, 14% of Chinese, and 57% of Oceanians are CYP2C19 intermediate metabolizers (IM). Clopidogrel efficacy is also reduced in individuals who are CYP2C19 intermediate metabolizers (IM). These individuals carry one CYP2C19 loss-of-function allele and one allele with normal or increased function. The frequency of the IM phenotype exceeds 45% in East Asian individuals, 40% in Central-South Asian individuals, 36% in Oceanian populations, about 30% in African individuals, 20–26% in American, European, or Middle Eastern individuals, and slightly below 20% in Latin individuals. The clopidogrel technical sheet approved by the FDA in 2022 includes a boxed warning on the reduced antiplatelet effect of clopidogrel in CYP2C19 PMs. The warning states that tests are available to identify individuals who are CYP2C19 PMs and to assess the use of another P2Y12 platelet receptor inhibitor in individuals identified as CYP2C19 PMs.

In 2025, the *Società Italiana di Genetica Umana* (SIGU) established a Pharmacogenomics Working Group with the aim of proposing principles and guidance for the standardization of the management and reporting of germline pharmacogenetic tests in Clinical Genetics services within the Italian NHS [106a]. It is desirable that multidisciplinary working groups can elaborate a better planning of PG test delivery modalities, which should not only include the possibility of continuously aligning reimbursable tests with drug regulatory agency recommendations, but also regulate the delivery of these services through legislation more closely aligned with the real situation. It is undeniable that pharmacogenomics has emerged and evolved as a discipline that, although related to medical genetics, encompasses diverse competencies such as clinical pharmacology, clinical biochemistry, and molecular biology.

3.3.2 Reimbursement and appropriate use of PG tests: issues, solutions and perspectives

The legitimate need to limit the markers present in the LEA nomenclature probably stems from the observation of uncontrolled and inappropriate demand for PG tests charged to the SSN, previously requestable with generic codes (e.g., 91.30.3, DNA segment analysis by sequencing). However, this configuration entails a series of limitations and does not resolve some crucial problems. For example, the polymorphisms analyzed to perform the CYP2D6 test may vary from a few (the most frequent) to dozens, depending on whether basic or more advanced technology is available. Analyzing a larger number of markers makes phenotype prediction more precise, and therefore results from tests performed in different facilities (public or private) are not always equivalent. The same may occur for important pharmacogenes such as DPYD and UGT1A1. Moreover, the restriction of prescription eligibility to a single drug, although

following a reasonable principle, is perhaps too restrictive, excluding from the possibility of therapeutic personalization important and particularly relevant patient categories. In addition, keeping pace with technological and bioinformatic evolution, reimbursement of broad PG analytical panels should be envisaged, including simultaneously all major genetic markers of drug response (see Section 3.3.3). The variance observed in the frequency of PG markers in the general population, the severity of their functional effect, and their predictive power represent factors for prioritizing markers to be set as a minimum requirement of a complex PG panel. The completeness of such information, acquired in a single analysis, would allow guiding prescribing choices throughout the patient's clinical history.

In any case, beyond the sustainability of PG test delivery by the SSN, the vast private offer in the field of PG cannot be ignored, stimulated also by patient-initiated requests. It is therefore not rare for physicians to find themselves consulting—and therefore taking into account—a private laboratory report containing pharmacogenetic information. It is therefore desirable that institutions and regional and national health authorities produce clear regulations establishing analytical, reporting, and data-protection requirements that guarantee citizens and guide medical training to provide physicians with the skills needed to avoid misinterpretation of PG results and to communicate correctly to patients the meaning of PG variants. A phenomenon that must not be neglected is the fear that PG test results may induce in patients: notations such as "mutated," "non-functional," "deleted," or "poor metabolizer" can generate anxiety, as patients easily interpret the presence of a variant as a generic severe risk factor. If not properly managed, this phenomenon could even lead patients to fear taking drugs, reducing treatment adherence.

Rather than restricting the PG test offer, stakeholders should therefore aim to ensure the appropriateness of PG test requests and the appropriateness of result use. In a regulated and controlled context, it will truly be possible to measure how much and in which clinical settings PG application improves appropriateness in drug administration, i.e., their efficacy and safety. Priority actions are:

- **Implementing training plans** to prevent misinterpretation by physicians and to provide skills to explain to patients the meaning of PG variants. One of the main barriers to clinical adoption and/or correct use of PG tests is the limited familiarity of healthcare personnel with clinical indications and result use.
- **Standardizing reporting methods.** Standardization is necessary starting from the description of the marker itself. There are several ways to identify and denote a DNA sequence variation, such as chromosomal position (e.g., chr7:17467065 (GRCh38); chr7:17506689 (GRCh37)), the amino acid substitution resulting from the variation (e.g., V>F; Val>Phe), the position of the polymorphic nucleotide (e.g., c.2983G>T), the identifier from the main polymorphism database (dbSNP, e.g., rs1801268) , or the "star" nomenclature, which labels each variant with an asterisk "*" followed by a number (e.g., *2A). This variety of nomenclatures in fact constitutes a set of synonyms referring to the same variant, which can generate confusion and misinterpretation. It would therefore be appropriate to issue recommendations on the preferred way to identify PG markers and, in any case, to recommend indicating, with appropriate notes in the report, the synonyms of the markers analyzed. The same problem occurs for result reporting. The genotype may be reported (e.g., GG; this result could be reported as CC by a laboratory sequencing the complementary DNA strand); in this case, the report does not indicate which allele is the risk allele. The note "normal homozygote," "heterozygote," or "mutated homozygote" may be inserted; in this case, attributing the risk allele to "mutated" may be misleading, since some variants are advantageous in terms of drug efficacy and tolerability. For highly polymorphic genes, the predicted phenotype based on the obtained genotype may be reported as the result; this facilitates interpretation, but it should be recommended to indicate precisely in the report which allelic variants were analyzed. Consider two different PG tests analyzing CYP2D6: the first test analyzes only the most frequent variants, and the result is a normal metabolizer phenotype; the second test also analyzes rarer variants, and the result is a slow metabolizer phenotype. Formally, both results are correct, but the limits of the analysis (in this case, type and number of variants analyzed) should be clearly reported.
- **Issuing recommendations on how to use the result.** Beyond a few pharmacogenomic markers (mentioned above) for which clinical use guidelines are relatively clear, it is necessary to implement decision-aid tools that support prescribing choices based on PG; these tools range from (apparently) simple lists of substrate, inducer, or inhibitor drugs of major cytochromes or major phase-II enzymes to the implementation of bioinformatic tools for selecting active ingredients most compatible with a patient's pharmacogenomic profile.
- **Clearly defining appropriateness criteria for PG test requests.** As also envisaged by the PROPHET working group, to favor effective integration of PG tests into clinical practice, national guidelines should be developed, adapted from major international organizations such as the Dutch Pharmacogenetics Working Group (DPWG), CPIC, and

others, to ensure recourse to available tests based on evidence and homogeneous across the national territory. Some recent works analyze discrepancies between pharmacogenetic indications reported in the Summary of Product Characteristics (SmPC) among different drug regulatory agencies, further highlighting that the different ways of classifying marker utility is an issue that must be addressed jointly at the international level. With regard to complex PG tests, it would be desirable to anticipate user needs by defining, through a review of the scientific literature, criteria for selecting patients for whom a multigene PG test (containing all major PG markers) should be requested, such as treatment-resistant patients (defined according to specific disease criteria) and patients with multimorbidity and polypharmacy.

- **Informing the public.** The success and acceptability of PG tests depend strongly on patients' level of awareness, understanding, and trust. Information campaigns and targeted communication strategies are needed to increase understanding of the benefits and limitations of tests, to avoid unjustified fears or false expectations. Ethical and privacy implications should be better managed through clear informative notes and structured informed consent to ensure that patients fully understand the purposes and implications of undergoing a pharmacogenetic or pharmacogenomic test, which, although belonging to genetic tests, differs substantially from tests aimed at diagnosing genetic diseases.
- **Improving access to PG tests and monitor result quality.** The reliability and quality of PG tests depend on the presence of well-equipped laboratories operating according to rigorous technical and quality standards. Regional inequalities in laboratory capacity still represent a significant challenge, especially in southern Italy and the islands, where access to tests is more limited. Strategic investments are needed to ensure equitable access to PG across the national territory, strengthening laboratory infrastructures and/or identifying high-throughput reference centers able to function as analytical hubs for samples from geographically distant areas (also exploiting the stability of biological samples, which facilitates storage and transport). In the perspective of an accreditation system for public and private laboratories providing PG tests, it is already possible to incentivize laboratory participation in external quality assessment programs. At the same time, regulatory and funding mechanisms should be established to encourage private companies to develop validated pharmacogenomic diagnostic kits. These tools would strengthen the national technological offer, favoring the availability of quality and sustainable diagnostic solutions for the healthcare system.
- **Achieving "portability" of PG data.** The analytical results of PG tests, especially when using advanced technologies such as next-generation sequencing (NGS), are produced in different raw data formats depending on the instrumentation used and therefore require an IT interface to transcode them into a proper genotype. Moreover, results are increasingly interpreted with the aid of bioinformatic software, which will soon be replaced by full-fledged artificial intelligence systems. It is therefore necessary that the various information systems used for the production, processing, transmission, and interpretation of pharmacogenomic data are interoperable, i.e., able to communicate through the same IT language, and able to interface with clinical data systems (electronic health record, clinical record, laboratory information systems, etc.).
- **Investing in research.** Further studies are needed to evaluate the clinical effectiveness and cost-effectiveness of multigene panels and clinical decision-support systems (CDSS). These studies should reflect the complexity and heterogeneity of the real context, involving different clinical settings and target populations. In particular, economic evaluations based on data from real-world implementations are needed to guide strategic planning and long-term policy decisions. International collaborations, for example modeled on the U-PGx project, are essential to produce robust and generalizable evidence across different healthcare settings and patient groups. This approach will support the development of more informed and scalable PG strategies.
- **Implementing a monitoring and evaluation system for the use of PG tests** and for the impact of their use on drug prescriptions and on the patient themselves, identifying specific indicators.
- **Fostering the development of bioinformatic supports for clinical decision-making guided by PG data:** it is necessary to integrate the functionalities of software developed for pharmacological interaction analysis to allow evaluation of the expected clinical effect of the presence of one or more PG variants. Interpretation frameworks should evolve together with progress in CDSS and scientific knowledge.

3.4 *Therapeutic Drug Monitoring*

Therapeutic Drug Monitoring (TDM) essentially consists of measuring the concentration of a drug in an easily accessible biological matrix, almost always blood, but also cerebrospinal fluid, urine, or breast milk. It is a tool that has been used for years to optimize and individualize the different stages of treatment and constitutes an essential instrument of Precision Medicine and Prescriptomics, as it allows monitoring of drug levels and adjustment of dosage to maximize efficacy and avoid toxic effects, as well as to verify adherence to therapy. In recent years, the list of active ingredients—and some important metabolites—that can benefit from TDM has increased considerably: it is now possible to measure psychiatric and neuropsychiatric drugs, cardiovascular drugs, antibiotics, antivirals, immunosuppressants, anticancer drugs, and biologic drugs. Not by chance, in the latest revision of the LEA nomenclature, the possibility of performing drug assays at the expense of the SSN has been greatly expanded.

In general, the following situations can be identified as circumstances in which requesting a blood drug assay may be appropriate:

- when using drugs with a narrow therapeutic range (i.e., a small difference between subtherapeutic, therapeutic, and toxic concentrations);
- when the therapeutic response is inadequate or a change in the patient's clinical status is observed;
- when treating "complex" patients (with organ excretory failure, undergoing dialysis, obese, gastrectomized, on polytherapy, etc.) or "special" patients (of different ethnicity, pregnant or menopausal women, very elderly patients, pediatric patients);
- when toxicity is suspected;
- when adherence to therapy needs to be verified;
- when there are potential interactions with other concomitantly administered drugs;
- when pharmacogenomic variants associated with altered pharmacokinetics of the administered drug are present; the functional effect of a genetic variant on drug metabolism can vary from patient to patient, as the phenotype is also determined by other factors that are not always identifiable.

Within these indications, however, a further assessment of the appropriateness of TDM as a tool for therapy management is required. A meta-analysis of clinical trials on the efficacy of TDM for managing antibiotic therapy in critically ill patients (septic or in intensive care) showed no significant improvement in clinical outcomes between patients monitored with TDM and those who were not. This finding confirms the need to improve guidelines for selecting patients who can truly benefit from drug assays.

A reference model is provided by the recommendations developed in the field of psychiatric TDM with the document "AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: update 2011" [111–113]. The relevance of TDM in psychiatry, with consolidated experience over many years of use, has indeed catalyzed efforts toward systematizing the TDM process, encompassing all major steps aimed at ensuring the cost-effectiveness of the methodology. The guidelines therefore include:

- specific indications for TDM in psychiatry (which drug and in which situation it is useful to request the assay), differentiated into multiple levels (strongly recommended, recommended, useful, potentially useful);
- reference therapeutic ranges ("therapeutic windows") and reference dose-correlated ranges, as a guide for laboratories and clinicians in psychopharmacotherapy;
- alert thresholds for laboratories, to warn physicians and patients when a concentration is detected that puts patient safety at risk;
- recommendations for operators performing the analysis (sampling method, sampling time, interpretation of results, and reporting);
- indications on clinical management of patients whose results fall outside reference intervals;
- recommendations regarding the combination of TDM and pharmacogenetic testing.

On this model, shared guidelines should be developed for other pharmacological areas, building on and refining proposals already available at the international level, in which some limitations have been highlighted [114–120]. Among these, the level of evidence for the need for TDM has sometimes been considered insufficient, suggesting the need to acquire more robust cost-effectiveness data.

On the other hand, there is fragmentation of the TDM services available across the national territory, both in terms of geographical distribution and in the number and type of measurable drugs. It therefore appears necessary to conduct a survey of needs and active services, in order to ensure uniform delivery of services included in the LEA and, at the very least, to guide physicians and patients toward facilities that provide TDM.

The role of TDM in Precision Medicine will undoubtedly become increasingly important, considering that software is already being developed for personalized dose prediction that, starting from concentrations measured with TDM and integrating other patient-specific data, is able to estimate appropriate doses to reach a predefined therapeutic target. In the near future, such software will also be able to correlate drug concentration with the pharmacogenomic profile and other predictive markers of response, including data on target receptor occupancy (obtained through imaging).

3.5 Multidisciplinary approach and telemedicine

Integrated patient management lies at the core of Precision Medicine, and it is no longer conceivable that a multidisciplinary approach to the patient be limited to healthcare facilities where multiple clinical specialties and innovative resources and competencies (pharmacologists, pharmacogenomics experts, advanced diagnostic laboratories) are co located.

Teleassistance and video visits are tools that can facilitate the phases of therapeutic optimization and reconciliation, while telemonitoring is poised to become an increasingly powerful means of verifying critical parameters in real time in complex patients, providing an alert system regarding the efficacy and safety of pharmacological treatments. Teleconsultation is emerging as an essential tool to support physicians working in community settings in the correct use of innovative resources such as pharmacogenomics, the evaluation of interactions in complex therapies, and therapeutic drug monitoring. Especially during a transition period in which Precision Medicine services are concentrated in a few centers of excellence, the simplest and most effective way to increase accessibility for users (both physicians and patients) is a widespread telemedicine system that, for example, allows requesting a pharmacological and/or pharmacogenomic consultation from a reference center.

Thanks to PNRR funding, a plan managed by AGENAS, in its role as the National Agency for Digital Health (ASD), was launched in 2023 to implement the National Telemedicine Platform, composed of a National Infrastructure and 21 Regional Infrastructures. ASD has defined the infrastructural requirements and interoperability characteristics required of regional platforms to ensure uniformity of services and performance, publishes guidance documents, PDTA, and protocols to facilitate the correct delivery of telemedicine services, provides user support, and monitors usage data. The implementation plan is in a phase of service launch and consolidation, with full operation expected in the coming years.

It is desirable that, during this period, digital PDTA specifically aimed at managing complex pharmacological therapies be developed, including therapeutic optimization and reconciliation activities, with pharmacological and pharmacogenomic consultation as key elements.

4. Indicators of prescribing appropriateness: tools for patient centered medicine

Identifying systems to measure and evaluate prescribing appropriateness is the first step toward taking actions aimed at improving it. Measurement and evaluation, even in the case of drug prescribing, must rely on “indicators,” i.e., measurable variables allowing a synthetic assessment/evaluation of complex phenomena and provide the elements necessary to guide decisions.

Indicators are therefore useful for comparing a phenomenon over time (at different moments) and in space (between different contexts). However, the purpose of these evaluations should not be to produce ranking reports (for example, among physicians or healthcare facilities), but to support improvements in prescribing practice through the implementation of appropriate strategies. For this reason, it is essential that the measurement of indicators is followed by audit sessions.

Prescribing appropriateness is certainly influenced by the sociodemographic context, specific healthcare characteristics, and the clinical complexity of the patient. These aspects must be taken into account when performing measurements, considering them as variables within a more complex process. Moreover, any change in these variables should translate into a measurable clinical benefit through specific outcome indicators. Consequently, it is important that studies are conducted to verify the association between process indicators of prescribing appropriateness and clinical and economic outcome indicators.

A non-secondary aspect is the applicability of prescribing appropriateness indicators to different settings (for example Regions and Local Health Authorities -ASL). To this end, the broad and widespread availability of administrative health data of the Italian NHS, allows the creation of prescribing appropriateness indicators reproducible in all settings, thus providing valid support for drug policy and clinical pathway management. However, there are several intrinsic limitations of this data source that must be considered when creating and interpreting prescribing appropriateness indicators. The wide availability of data, particularly those relating to drug dispensing covered by the SSN, over time has led to the development of a large number of prescribing appropriateness indicators, sometimes redundant and with limited impact on clinical practice. In some cases, this proliferation has reduced the perceived value of these measurement tools, which are often viewed by physicians as instruments for controlling their work rather than as tools for improving their clinical practice. To avoid this, it is important to carefully select the indicators to be used. A first consideration is that indicators are often referred to as indicators of appropriateness, but in reality “inappropriateness” indicators are often used, as available evidence is not always solid, and it is often easier to identify prescribing behaviors that should be minimized instead of those that should be encouraged. Another aspect to consider in constructing appropriateness indicators is the level of application of the indicator, depending on whether it refers to the single case or to the entire population. Finally, in the construction and evaluation of appropriateness indicators, it is important to consider patient characteristics and the healthcare setting. It suffices to consider how the results of appropriateness indicators may differ between healthy elderly patients living at home and those residing in assisted-living facilities or hospices.

Below, the main experiences related to prescribing appropriateness indicators developed by Italian health institutions are analyzed, highlighting their strengths and weaknesses and suggesting possible improvement strategies, with the aim of making these tools increasingly effective and ensuring their correct interpretation.

NSG LEA System

The main initiative of the Ministry of Health in the field of indicators for healthcare is represented by the “New Guarantee System for Monitoring Essential Levels of Assistance” (NSG LEA), introduced with the Ministerial Decree of 12 March 2019. Among the various indicators of the NSG LEA system, two concern prescribing appropriateness. In particular, for patients affected by COPD, an indicator of appropriateness and adherence to pharmacological treatment with long-acting bronchodilators (Long-Acting Beta2 Agonists – LABA as monotherapy; Long-Acting Muscarinic Antagonists – LAMA as monotherapy; LABA + LAMA; LABA + LAMA + inhaled corticosteroids – ICS) has been identified, calculated over 12 months of observation. This indicator was created with the aim of verifying the homogeneity of the main pharmacological treatment offered for COPD. Similarly, an indicator of appropriateness and adherence to treatment with ACE inhibitors or sartans, and treatment with beta-blockers for patients with heart failure, has also been identified. The rationale underlying this indicator is the need to verify the homogeneity of the pharmacological treatment offered for heart failure, in the awareness that adequate therapeutic coverage is correlated with a reduction in the risk of re-hospitalization after diagnosis and/or the risk of death. However, in both cases patients are identified using hospital discharge records and therefore cannot be considered representative of the entire population affected by the disease.

Appropriateness indicators in OsMed

The annual report on medicines use in Italy, published by the Medicines Utilization Monitoring Center (OsMed) of the Italian Medicines Agency (AIFA), is the main source where prescribing appropriateness indicators developed by a central health institution can be found.

Traditionally, the OsMed report includes a specific section presenting a set of indicators for evaluating the appropriateness of use of the main categories of drugs prescribed in the general practice population. These refer to drugs for cardiovascular risk prevention (for example, antihypertensives and lipid-lowering agents), drugs for obstructive respiratory diseases, antiacid/antisecretory/gastroprotective drugs, antidepressants, sedative-hypnotics and anxiolytics, and drugs for the treatment of osteoporosis. In addition to indicators based on general practice databases, the OsMed report has always included appropriateness indicators - with a specific focus on adherence and

persistence - for various therapeutic categories based on administrative databases. These indicators are constructed using the database of prescriptions for class A drugs dispensed at the national level for the treatment of major chronic diseases.

AIFA Notes

Introduced in 1993 following the establishment of the new Therapeutic Formulary (Law No. 537 of 24 December 1993) of the NHS, initially drafted by the Italian National Drug Commission (CUF), the AIFA Notes define the therapeutic indications for which certain medicinal products are reimbursed by the SSN. They have become a regulatory tool aimed at ensuring the appropriate use of medicines, guiding physicians' prescribing activity based on the best evidence of efficacy available in the literature. Notes may be issued when a drug is authorized for several clinical indications, only a subset of which is relevant, or when the drug is used to prevent a significant risk in specific population groups. They may also be introduced when the medicinal product is prone to potential improper uses that fall outside proven efficacy or in ways that could diminish its safety profile. The process of revising and updating the Notes is continuous, based on the availability of new scientific evidence, making this regulatory instrument flexible and capable of responding to the needs of everyday medical practice across the national territory. The purpose of such revisions is to simplify and streamline patient management, improve consistency between indications supported by robust evidence and those eligible for full SSN reimbursement, and prevent improper use or significant risk for one or more population groups. The AIFA Notes currently in force are 39, compared to the 71 initially introduced by CUF in 1994 with the drafting of the new SSN Formulary and the reclassification of drugs, pursuant to Article 8, paragraph 10, of Law No. 537 of 24 December 1993.

The need to integrate administrative data with clinical and socio-health data

In light of the experiences described and the limitations of systems for measuring appropriateness indicators, several critical issues currently prevent the full contextualization of these indicators within a more complex process. These issues stem from the nature of the data source generally used by health institutions to construct appropriateness indicators: administrative health databases. These databases, present in all Regions and ASLs, have the advantage of being interconnected, allowing patient tracking across different accesses to the SSN, but they lack a series of clinical information. This deficiency can undermine the clinical meaning of the indicator itself and compromise its validation, i.e., the verification of the association between process and outcome. For example, the lack of clinical information in this data source does not allow accounting for the severity of a given disease or for knowing the exact indication for which the drug was prescribed. Therefore, to correctly consider appropriateness indicators within a pathway, it is necessary to integrate administrative health data with additional data capable of conveying severity and fragility information (for example essential clinical data, laboratory test values, including those derived from multidimensional assessment for fragile individuals, and the specific indication underlying the prescription). To achieve this objective, in the immediate future it will be necessary to identify, for major chronic diseases, a "minimum clinical dataset" containing the essential clinical variables to be included in administrative databases. In addition to clinical information, given that lack of prescribing appropriateness is a multidimensional phenomenon influenced by various determinants, it is important to also take into account social and organizational variables when evaluating indicators that describe it. To this end, it would be useful to integrate health information with social information (for example, income situation, deprivation conditions, lifestyle). In conclusion, only by achieving real integration of all available data will it be possible to construct indicators capable of providing an accurate measure of prescribing appropriateness, thereby appropriately guiding drug policy choices, supporting physicians in their clinical practice, and placing the real needs of the patient at the center, ultimately ensuring proper therapeutic management.

5. Prescribing appropriateness and correct use of medicines: from the patient's perspective

5.1 Participatory medicine: involving patients in the care process

Bury [126] highlights how, during the 19th century, before the advent of modern medicine, the physician's ability to understand disease was strongly linked to their capacity to listen to, interpret, and collect the patient's story. For physicians it was essential to gather information about the patient's lifestyle, past history, living and working environment, and beliefs. At the time, this patient-oriented approach was fundamental, given the limited physiological

and anatomical knowledge and the absence of the diagnostic tools now available to professionals. The diagnostic pathway, as defined today, was based on prior knowledge and new information obtained from listening, not only from examining the patient. However, with modernization and socioeconomic progress, two opposite trends have emerged in the physician–patient relationship. Physicians face increasing pressure due both to organizational deficits and to the high degree of specialization achieved by medical sciences, which fragments care pathways (due to a lack of adequate integration strategies), progressively reducing the time available for interaction with each patient. On the other hand, the level of medical literacy in the general population has grown enormously, as has awareness of the right to health, leading to a change in patients' attitudes toward healthcare professionals. Today, patients-citizens increasingly refuse to accept medical decisions, as they did in the past, as unquestionable truths, and instead assert their right to understand and share the reasons behind them, as well as to evaluate and, if necessary, challenge the quality of the healthcare services received. At the same time, the large volume and high visibility of uncontrolled, incorrect, and misleading medical information accessible to the population have generated a perverse mechanism that fosters distrust and unrealistic expectations toward healthcare professionals, who in turn are induced to adopt defensive medicine to prevent medico-legal actions.

It is therefore necessary to restore a physician–patient alliance at the interpersonal, social, and organizational levels, enabling the patient to feel a subject, and not an object, in the management of their own health. With this aim, efforts have been made for several years to promote the development of "Participatory Healthcare" (or "Participatory Medicine"), where citizens are integral and active participants in decision-making processes at both the individual and organizational levels, giving rise to the so-called "patient involvement."

Active patient involvement is recognized as one of the seven strategic objectives of the WHO Global Patient Safety Action Plan 2021–2030, which aims to eliminate avoidable harm in healthcare, increase patient satisfaction, and improve health outcomes. It includes the processes of "patient empowerment" and "patient engagement." "Patient empowerment" refers to the set of actions through which the patient is informed and educated so as to understand the reasons and possible outcomes (positive and negative) of healthcare treatments, as well as the possible consequences of refusing treatment, thereby acquiring the ability to participate consciously in medical decisions concerning themselves. Empowerment develops and consolidates into "patient engagement," i.e., the patient assuming a more active role in maintaining health or managing disease.

These two aspects manifest both at a personal level, concerning the individual physician–patient relationship and thus calling on healthcare professionals to adopt practices that actively involve the patient, and at a systemic level, requiring actions by healthcare stakeholders aimed at:

- communication, understood as a bidirectional activity capable of capturing primary needs for general and in-depth information and responding to them effectively and promptly;
- training healthcare professionals in correct interpersonal communication methods;
- issuing procedures and recommendations aimed at standardizing how active patient involvement is implemented in their care pathway, as well as the tools needed to measure and evaluate healthcare performance as perceived by users.

Within the context of personalizing and improving the appropriateness of pharmacological prescriptions, patient involvement can positively influence known factors that reduce the effectiveness and safety of medicines, in particular adherence to therapy and correct drug use, as shown by several relevant meta-analyses [129–131].

The space devoted to listening to the patient is key to their involvement, as it first allows identification of the patient's level of awareness of their condition and their ability to understand medical language, and then enables adaptation of the communication style and the type of information to be conveyed. Effective communication, by clarifying expectations, treatment stages, and therapeutic objectives, reduces stress and anxiety, facilitates better day-to-day management of therapy and strengthens the patient's capacity to detect both potential and real emergency situations. In certain specific areas, it is also extremely important to interact positively with caregivers: for example, in psychiatric, neurodegenerative, and pediatric conditions, the caregiver's anxiety and concern—often coupled with partial responsibility for the patient's adherence to prescriptions—requires an integrated management approach supported by a network of psychological, social, and educational support, which is unfortunately often lacking or fragmented.

With regard to drug intake, dialogue with the patient (and caregiver) is an effective tool for identifying and addressing many causes of non-adherence to therapy:

- fear of side effects, when freely expressed, can be mitigated by explaining the possible consequences of not taking the drugs, sharing risk/benefit assessments with the patient, and quantifying the patient's actual risk of experiencing side effects or adverse events compared with the real risk of health deterioration;
- stigma associated with certain drugs, for example psychotropic medications, can be countered by explaining the mechanisms of drug action;
- fear arising from false beliefs, such as the perceived danger of certain treatments, can be discussed in relation to the most authoritative information sources;
- lack of conviction about the usefulness of drug intake, especially when administered for preventive purposes, can be countered by a simple explanation of the scientific rationale of the treatment;
- the need to take drugs in specific formulations or at specific times, or too many times per day, can be made less burdensome by accommodating, where possible, the patient's preferences and grouping intake as much as possible at the same time;
- more or less accidental and frequent forgetfulness or errors in drug intake can be significantly reduced by providing clear tables indicating how and when to take the drugs, which can also serve as an adherence diary that encourages the patient and/or their caregivers to be more attentive.

Likewise, dialogue with the patient is the privileged way to identify incorrect use or administration of drugs:

- administration errors due to poor patient understanding of the physician's instructions (timing, relation to meals, dosage) can be minimized by using the "teach-back" method , i.e., asking the patient to repeat in their own words what has been explained about the therapy to verify understanding, and by providing printed reminders with times, modes of intake, and dosage;
- encouraging the patient to describe their habits regarding self-medication is important, as it is a major source of inappropriate drug use and an opportunity to provide targeted information about the appropriate use of over-the-counter medicines.

Using the patient's narrative as a support for medical decisions thus becomes a strategic tool for personalizing treatments and is known as "narrative medicine," a methodology that originated with Arthur Kleinman's publication *The Illness Narratives* (1988) and has been extensively developed by Rita Charon, an internist at Columbia University. In the modern world, narrative medicine should not be understood only as a mental attitude of the physician, but also as a medical competence requiring specific training, to be used complementarily to Evidence-Based Medicine (EBM). Indeed, in physician–patient conversations two different perspectives often meet and sometimes clash: what the patient experiences (illness) and the diagnosis made by the physician (disease). The illness–disease dyad must be reconciled through holistic patient assessment achieved via listening and dialogue.

At the level of direct interaction with the patient, the main barriers that hinder patient involvement are:

- time constraints: the time needed to obtain a precise picture of both the patient's health status and the personal, social, and environmental factors that may influence treatment success is often not provided for in clinical practice. This is certainly one of the major barriers preventing patient involvement and their perception of receiving the expected care and attention
- barriers to mutual understanding: clinicians often assume that patients understand even complex medical terms; this barrier is accentuated in specific situations such as foreign patients with limited knowledge of the clinician's language, physical disabilities that prevent normal oral communication, or intellectual disabilities that partially inhibit communication. In all these cases, linguistic or communicative mediation must be provided, ensuring that both oral and written communications are comprehensible. In the case of people with disabilities, it is important to respect their right to self-determination (established by the UN Convention on the Rights of Persons with Disabilities) and not to immediately turn to the caregiver, thereby excluding the patients from decisions concerning them
- underestimation of cognitive, emotional, cultural, and social aspects that influence the patient's attitude.

All this reflects a broader phenomenon that constitutes an organizational barrier to be overcome and leads to poor communication even when the physician is fully aware of the need to actively listen to the patient's experience and share therapeutic decisions.

A fundamental role in removing this barrier is played—and should be more widely recognized—by patient associations, which elevate patient engagement to the social level by participating in decision-making, presenting to other stakeholders the real and most urgent needs of citizens, acting as cultural and communicative mediators between healthcare professionals and citizens, and providing additional or enhanced services, including psychological support often lacking in hospital settings but characteristic of many associations. In 2021, the Ministry of Health established a working group on participatory healthcare, which concluded with a guidance document [135a] aimed at defining the roles and modes of participation of citizen associations in the planning and management of health interventions and services. An amendment to the 2025 Budget Law provides for the establishment of a Single Register of Health Associations (RUAS), whose members will be able, among other things, to participate in consultations of AIFA's Scientific and Economic Committee. Implementing decrees for this amendment are awaited.

It is clear that the organizational and functional differences characterizing various healthcare settings require different approaches to increase patient participation, also in line with the real resources available. However, the multiplicity of existing tools to promote active involvement of the patient and their caregiver allows them to be applied in varied and targeted ways to specific structural and organizational needs. While some of these tools require greater resource investment, others can be implemented in a very simple and inexpensive manner, and their systematic application requires, more than additional resources, only greater synergy among healthcare stakeholders.

Tools for communication

- *Specific education for healthcare professionals:* communication is a fundamental function of the healthcare professional, and specific education on this topic should become a primary objective for stakeholders involved in healthcare training, management of healthcare facilities, and professional societies and associations, as well as an evaluation criterion for both the healthcare facilities where the professional works and for users of those facilities. Behavioral approaches to the patient, such as "goal setting," i.e., the shared definition of clear, realistic, and personalized health goals, or "motivational interviewing," a method to motivate patients to adopt appropriate behaviors and follow prescribed treatments, must be supported by both specific training and organizational models that facilitate their application.

- *Specific education for patients/caregivers:* health literacy programs, in addition to conventional informational resources, should encourage the development of interactive group training sessions aimed at equipping patients and caregivers with the skills needed to better manage their own condition or that of their relative and to openly address their doubts and concerns. This type of intervention is particularly valuable in the case of chronic diseases or conditions involving some form of disability.

- *Written communication:* the importance of written communication with the patient - rich in opportunities often underused - should not be underestimated. Providing patients with printed rather than handwritten instructions, and with pre-printed or printed reminders containing basic and/or personalized information constitutes a simple and universally accessible tool that has the potential to resolve doubts and avoid repeated requests for clarification.

- *Decision-aid tools and patient portals:* it is important to share with the citizen-patient the factors guiding clinical decision-making, clearly explaining the rationale for treatments, their actual risks and benefits, and the alternative options available. Equally essential is the coordination - among major health authorities, scientific societies, and patient associations – of the production and dissemination of brochures, videos, apps, and online resources (e.g.: Mayo Clinic, **https://www.england.nhs.uk/personalisedcare/shared-decision-making/decision-support-tools/**).

Digital tools supporting the patient

- *Health-management apps:* the digital era has seen an uncontrolled proliferation of mobile applications dedicated to health management. They can provide fundamental support, for example by reminding patients to take their medicines correctly and continuously, indicating how to take them, and suggesting foods or drinks to avoid or favor during pharmacological treatment or in the presence of specific pathological conditions. However, it would be desirable for

major regional or national health institutions - co-designed with patient associations - to develop non-commercial apps in order to provide an authoritative source of information free from potential commercial interests and based on recognized scientific evidence.

- *Wearable devices:* wearable devices are also becoming increasingly widespread and useful for managing pharmacological therapies, reminding patients to take prescribed medicines or monitoring vital parameters that may be influenced by treatments, and encouraging patients to actively manage their own health. However, in this case uncontrolled use must be avoided: false alarms or misinterpretation of data can generate anxiety and lead to errors in drug intake. It would also be useful to guide patients both in choosing reliable devices and in learning how to use them correctly. Developing devices or apps capable of interfacing with the information systems used by physicians and healthcare facilities will offer in the future a real-time patient monitoring modality - although the information flow will need to be channeled and filtered (likely through AI tools) to prioritize relevant alerts.

Feedback and evaluation tools

Regularly asking patients and caregivers to provide feedback on their experience is essential to identify weaknesses in healthcare services, as shown by studies analyzing the role of user-derived indications in defining the appropriateness of clinical-organizational interventions (Caregiver-Patient Health Engagement Scale C-PHE). Increasing efforts are therefore being made to structure and systematize the collection of patient/caregiver feedback, particularly through the definition and promotion of Patient-Reported Outcome Measures (PROMs) to assess healthcare performance.

A Patient-Reported Outcome (PRO) is defined by the Food & Drug Administration (FDA) as “any report of the patient’s health status that comes directly from the patient without interpretation by a clinician or other party.” Similarly, the European Medicines Agency (EMA) defines PROs as “any outcome assessed by the patient themselves and based on the patient’s perception of a disease and its treatment”.

The corresponding outcome measures (PROMs) are usually used, both in clinical practice and in research, in the form of surveys or questionnaires to capture the patient’s perspective on a range of issues, including symptom severity, treatment side effects, psychological problems, treatment satisfaction, and health-related quality of life.

Collecting these measures enables identification of discrepancies between expected treatment outcomes and the improvements actually perceived by the patient, as well as ongoing monitoring of symptoms and side effects. At the managerial level, PROM data provide insights into the quality of healthcare services offered, allowing identification of shortcomings in specific phases of the care pathway (for example, reception, staff relationships, service accessibility). PROMs can be divided into generic and specific measures.

Generic PROMs are not specific to a disease, condition, or treatment but can be used across different pathologies. They generally capture cross-cutting quality-of-life domains such as the ability to perform daily activities, mental and emotional well-being, the ability to maintain social relationships, and pain. They are particularly valuable in economic evaluations, as they can be used to derive utility values related to health status, which can then be incorporated into the calculation of Quality-Adjusted Life-Years (QALYs).

Specific PROMs are designed to assess the severity of symptoms or functional limitations specific to a particular health condition. Compared with generic outcome measures, they tend to be more sensitive and allow evaluation of detailed aspects relevant to specific diseases or patient groups, ensuring a more accurate measurement of disease impact and treatment benefits. This makes them particularly useful, for instance, in rare diseases, where patient needs may differ significantly from those of the general population. Incorporating the patient perspective through PROMs - especially where unmet needs are high and data may be limited - can help capture treatment effects, strengthen available evidence, and support more informed clinical, regulatory, and economic decision-making.

Although PROMs represent an important source of evidence for measuring perceived benefits and risks, their use remains fragmented and poorly standardized. Data are heterogeneous and therefore have limited utility overall.

Ensuring that PROMs are valid, reliable, and meaningful across various diseases requires a collaborative approach among researchers, clinicians, patients, and regulatory authorities.

5.2 Adherence to therapies

As mentioned, the active involvement of the patient in managing their own therapeutic pathway is a crucial element for improving adherence to therapies, with a direct impact on treatment efficacy and safety. The concept of "adherence" refers to the extent to which a patient follows medical prescriptions, which include not only the regular intake of medicines, but also active participation in monitoring their own health status and in managing treatments. Therapeutic compliance is fundamental to achieving positive outcomes in the treatment of chronic diseases, but also in acute situations where correct drug management can mean the difference between therapeutic success and failure.

Despite the importance of good adherence, several studies have shown that a significant proportion of patients do not follow medical prescriptions correctly, with negative impacts on clinical outcomes, safety, and the healthcare system as a whole. A low level of adherence can seriously compromise therapeutic efficacy, leading to inadequate disease control, an increased risk of complications, and a greater likelihood of hospitalization. For example, non-adherence to drugs for chronic diseases such as hypertension and diabetes can increase the risk of adverse events, such as stroke, myocardial infarction, or renal failure. Moreover, poor adherence is often associated with a higher incidence of side effects, which may arise from ineffective treatment or incorrect dosing. Improving adherence to therapy can significantly reduce healthcare costs, minimize hospitalizations, and improve clinical outcomes.

It is therefore necessary to identify the causes of low adherence and to provide physicians with tools to assess and minimize the risk of non-adherence, and patients with tools that facilitate correct and continuous therapy intake.

The main critical points that hinder adherence to therapy are:

1. **Complexity of the therapeutic regimen:** a complex pharmacological regimen, with multiple drugs and administration times, is one of the main obstacles to patient adherence. Many patients - especially the elderly and those on polypharmacy - struggle to follow prescriptions correctly, resulting in reduced treatment efficacy.
2. **Psychological and social barriers:** factors such as lack of motivation, fear of side effects, low trust in therapies or in the healthcare system, and the perception of not being involved in the care process, reduce compliance. The psychological aspect plays a key role, since patients who do not fully understand the importance of therapy are less likely to follow it.
3. **Inadequate communication between physician and patient:** ineffective communication or the inability of healthcare professionals to adapt explanations to the patient's needs can create confusion about therapeutic instructions. A lack of clear communication may lead to incomplete understanding of the treatment and lower adherence.
4. **Multiplicity of therapeutic plans (TP) for a single patient with multimorbidity:** having multiple therapeutic plans can represent a barrier to accessing treatments and can interfere with adherence, in addition to increasing the workload for healthcare personnel in prescribing centers. In this context, maximum bureaucratic simplification (for example, adopting a single TP for the same class of drugs used for different indications) and dematerialization of TP renewal processes - removing unnecessary barriers - would be desirable.

At the same time, several solutions to improve therapy adherence are easily implementable:

a) **Monitoring adherence:** to improve adherence, it is essential to constantly monitor correct drug intake. Advanced technologies such as electronic blister packs or "smart pills," which send notifications when drugs are not taken, can be useful for tracking adherence and intervening promptly. In addition, smartphone apps that remind the patient when to take the drug can support the management of complex therapeutic regimens.
b) **Patient support tools in therapy management:** another fundamental solution is the adoption of educational and support tools that strengthen the patient's understanding of the treatment and its long-term benefits. This includes personalized informational materials, educational videos, consultation sessions with the physician or pharmacist, the medical pharmacologist, and the use of virtual coaches. Continuous education helps overcome misinformation and encourages patients to make informed decisions about their health. Personalizing of treatment - considering individual preferences and circumstances - can increase patient motivation.

c) **Telemedicine and remote monitoring:** telemedicine, which enables remote consultations, can significantly improve adherence to therapies, especially in patients living in remote areas or with difficulty attending in-person visits. Receiving advice and resolving doubts remotely - without having to travel to hospital - reduces frustration related to disease management, improves interaction and medical support, and allows timely intervention in case of problems.
In monitoring adherence, the role of the community service pharmacy—a key pillar of local healthcare delivery, regulated by DM 77 and a series of more recent legislative measures—should be considered. Community pharmacies constitute the most capillary and proximate component of the care network in our country (over 15,000 nationwide) and represent, for citizens and especially in certain geographical contexts, the first point of assistance and, in general, the usual contact point for obtaining therapies. It is easy to imagine that a tele-monitoring system of therapeutic refills starting from the pharmacist and triangulated with the patient and the general practitioner, could substantially contribute to identifying discontinuities in adherence to therapies. Likewise, the community service pharmacy, through the provision of diagnostic services (point-of-care tests, ECGs, ECG and blood-pressure monitoring), will increasingly support the assessment of therapy effectiveness and the achievement of therapeutic targets - currently widely unmet in chronic diseases, especially cardiovascular ones.

d) **Involvement of the patient's reference figures in the care pathway, with an active role:** the active involvement of the patient, facilitated by modern technologies such as adherence monitoring, telemedicine, and psychological and educational support tools, represents a winning strategy for reducing factors that hinder compliance. The integrated approach combining education, technology, and active monitoring not only improves clinical outcomes, but also contributes to more effective management of healthcare resources, reducing costs related to complications and hospitalizations.

Legislative intervention to support adherence monitoring and the achievement of therapeutic efficacy targets—bearing in mind that the purpose of adherence is to maintain the unchanged efficacy of therapies—appears necessary to counteract a phenomenon that, even in the latest OSMED 2023 report, emerges as a largely unmet clinical need. In this perspective, adherence and therapeutic efficacy indicators could be identified and included in the LEA for evaluating district-level care.

Collaboration between patients, patient associations, and healthcare institutions is fundamental to ensuring intervention policies that truly meet patients' assistance and care needs.

5.3 Correct use of medicines by the patient: risks of self medication

Self-medication is an extremely widespread and cross-sectional phenomenon in the general population. It includes the use of over-the-counter medicines, prescription-only medicines, supplements, and nutraceuticals without a specific medical indication, as well as the arbitrary modification of the mode of intake or the sudden discontinuation of a treatment prescribed by the physician. A recent survey reports that in Europe the practice has a prevalence of 34.4% and identifies demographic, social, and cultural determinants.

These behaviors can produce harmful effects, including adverse reactions, dependence, development of pharmacological resistance, masking of clinical symptoms, and worsening of a condition that has not been correctly diagnosed and treated.

A paradigmatic example of improper drug use is self-medication with antibiotics [145–147], which can be harmful both to the individual patient and to the community, directly contributing to the growth of antibiotic resistance. The causes include problems related to healthcare professionals, the organization of healthcare systems, and widespread misinformation among patients. If a clear cause of improper antibiotic use is the poor understanding by users of the drug target (limited distinction between viral and bacterial infections), the wide variability in bacterial sensitivity to specific antibiotics, and the etiological nature of clinical symptoms such as fever, pain, and inflammation - often wrongly attributed to infections - it is evident that communication between healthcare professionals, institutions, and health authorities has been inadequate and ineffective.

It should be noted that, while we have a clear picture of over-the-counter drug consumption, there is no system to verify the use of prescription-only medicines obtained by the patient on previous occasions. The therapeutic reconciliation activities described above, if integrated into an appropriate information flow, would allow the identification and correction of improper medicine use and the analysis of potential public-health implications. Identifying subgroups of patients in whom incorrect drug use prevails would also make it possible to define specific training needs and - through the contribution and cultural mediation of patient associations – to design targeted and widespread communication strategies aimed at protecting citizens' health.

6. Research priorities: Artificial Intelligence and Bioinformatics for Precision Medicine

Precision Medicine represents an epochal and irreversible transformation in the way we understand, prevent, diagnose, and treat diseases. Unlike the traditional **"one-size-fits-all"** approach, in which treatment is standardized according to population-level statistical categories, Precision Medicine is based on the principle that **each individual is a unique biological system**, with genomic, epigenetic, metabolic, environmental, and behavioral variables that cannot be reduced to an average.

This revolution is made possible by three technological pillars: **bioinformatics, artificial intelligence**, and **high-density computational capacity**. Together, these enable the processing, correlation, and real-time modeling of millions of biological and clinical data, transforming medicine from reactive to **proactive, predictive, personalized, and participatory (P4 Medicine)**.

In this scenario, **Artificial Intelligence (AI)** and **Bioinformatics** can no longer be considered merely auxiliary tools; they must be recognized as **epistemological engines**. They not only enhance the collection and interpretation of clinical data, but also **fundamentally reshape the ways in which medical knowledge is generated, validated, and applied**.

AI in Precision Medicine enables the construction of highly reliable predictive and decision-making models capable of identifying **diagnostic biomarkers** and **molecular patterns** not detectable by the human eye. Bioinformatics, in turn, allows the integration of heterogeneous domains—from whole-genome sequencing to gut metagenomics, from transcriptomic analysis to protein profiling — extracting clinically useful knowledge from complex data matrices (clinical-biological big data).

This integration between AI and bioinformatics is now a **necessary condition for ensuring the sustainability of a modern healthcare system**: sustainability in economic terms (reducing hospitalizations and the administration of ineffective medicines), but also in ethical and environmental terms. The responsible use of AI allows optimizing diagnostic and therapeutic resources, minimize waste and improve patients' quality of life. Its deployment is governed by a structured regulatory framework that imposes specific technical, ethical, and regulatory requirements. Key references include:

- **Regulation (EU) 2017/745 (MDR)** and **Regulation (EU) 2017/746 (IVDR)**: regulate medical devices and in-vitro diagnostic devices, including AI-based software. Any AI tool used to support diagnosis must undergo clinical validation, bear CE-marking, and comply with defined conformity assessment procedures.
- **EMA (European Medicines Agency) and FDA (Food and Drug Administration) guidelines** on adaptive algorithms and Software as a Medical Device (SaMD), in particular the FDA document "Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning-Based Software as a Medical Device."
- **International ISO/IEC standards**, such as:
    - **ISO/IEC 23053:2022** – Framework for Artificial Intelligence (AI) Systems Using Machine Learning;
    - **ISO 13119** – standards for structured electronic health records;
    - **ISO/TS 22692:2022** – technical specification for the application of AI in healthcare services.

- **The European AI Act** (Regulation in final approval phase in 2025), which classifies AI applications in healthcare as "high-risk," imposing obligations relating to transparency, technical robustness, data traceability, and ethical auditing.
- **The WHO Ethical Code for Artificial Intelligence in Health**, adopted in Italy by the Ministry of Health and **AGENAS**, which emphasizes explainability, non-discriminatory algorithms, equitable access, and protection of genomic-data.

The need to **develop personalized and dynamic clinical models** has also changed the nature of biomedical research. It is no longer sufficient to publish results in the literature; models and algorithms must be translated into clinically usable interfaces, interoperable with electronic health records, and updatable based on evolving real-world data.

From this perspective, AI and bioinformatics now determine the **priorities of public and private research**. Funding bodies—national and European—place at the center of thematic calls the construction of predictive platforms, integrated databases, computational trials, and clinical digital-twin projects. Programs such as **Horizon Europe, EU4Health, PNRR M6C2 – Digital Health**, and initiatives such as the **Genomic Data Infrastructure** or **EHDS (European Health Data Space)** are built precisely along this trajectory.

In the Italian context, the adoption of European strategies requires strengthening IRCCS networks, technological clusters (e.g., ALISEI, Lombardy Life Sciences), and training models such as BRIA (Bioinformatics, Immersive Reality, and Artificial Intelligence), which ensure the presence of human resources capable of operating with full awareness in the interdisciplinary domains of Precision Medicine.

6.1 What is Artificial Intelligence in Precision Medicine?

Artificial Intelligence (AI) applied to the medical domain should not be interpreted reductively as a mere tool for automating repetitive tasks or as an ancillary component of healthcare digitization. On the contrary, it represents a paradigm shift in the computational ability to extract knowledge from clinical, genetic, environmental, pathophysiological, and behavioral data of extremely high dimensionality. Today, AI in medicine constitutes the methodological bridge between an enormous volume of information—often scattered, heterogeneous, noisy, and temporally non-linear—and the concrete needs of clinical practice, ranging from early diagnosis to therapeutic personalization and the prediction of the evolution of chronic and complex diseases.

In the specific context of Precision Medicine, Artificial Intelligence assumes a systemic role. It becomes the cognitive interface between the physician and the biological complexity of the patient, acting as the operating system of an extended clinical intelligence, which integrates knowledge distributed across multiple levels—genomic, transcriptomic, epigenetic, radiomic, phenotypic—to generate validated predictive and prescriptive models. From this perspective, AI does not merely classify existing patterns; it actively contributes to uncovering latent relationships, providing explanations, and suggesting actions in real time and on an individual basis.

The AI technologies currently having the greatest impact in the healthcare sector, particularly in Precision Medicine, can be outlined as follows:

Machine Learning (ML) – enables modeling of complex relationships between inputs and outputs in environments characterized by high variability and incomplete data. Supervised techniques are used to train predictive models on annotated datasets (e.g., prediction of pharmacological response), while unsupervised algorithms allow the identification of new patient subgroups or disease subtypes through clustering. Reinforcement learning methods are increasingly applied to optimize therapeutic strategies in dynamic settings, such as adaptive drug administration in oncology or intensive care medicine.

Deep Learning – the use of deep neural networks, particularly Convolutional Neural Networks (CNN), has revolutionized imaging diagnostics. In radiology, AI can detect lung lesions, brain abnormalities, and breast microcalcifications with sensitivity comparable to—and in some cases exceeding—that of expert physicians. In computational histopathology, deep learning enables automatic analysis of digitized slides, facilitating the diagnosis of solid tumors. In genomics, models based on Recurrent Neural Networks (RNN) or Transformers are used to predict the functionality of coding sequences and to identify rare mutations with phenotypic impact.

Natural Language Processing (NLP) – a large portion of clinical information resides in unstructured text: clinical records, reports, discharge summaries, anamneses, and medical notes. NLP enables automatic extraction of clinical entities, coding of diagnoses, recognition of symptoms, treatments, and causal relations. With the advent of advanced models such as BERT, BioBERT, and medical-oriented versions of ChatGPT (e.g., Med-PaLM), clinical-language analysis has become essential for building dynamic knowledge bases and providing real-time decision-support systems.

Generative predictive algorithms – recent advances include **deep-learning-based generative models** capable not only of predicting a patient's future state, but also of generating **hypothetical clinical scenarios**, useful for simulating virtual trials, evaluating responses to treatments not yet administered, or estimating the efficacy of therapeutic combinations at the molecular level.

However, the effectiveness of Artificial Intelligence in medicine must be anchored to rigorous principles of **reliability, transparency, safety, and explainability**. AI solutions must be designed according to international safety standards for medical-software (IEC 62304), clinically validated according to Good Clinical Practice (GCP) protocols, and certified as **Software as a Medical Device (SaMD)** when used to support diagnostic or therapeutic decision-making. The new **European AI Act**, set to become the reference legal framework in the coming years, classifies AI applications in healthcare as **"high-risk,"** imposing stringent requirements for **explainability, data governance, human oversight**, and technical robustness.

In conclusion, Artificial Intelligence applied to Precision Medicine is not an incremental innovation, but **a true ontological change in medical practice**, redefining the relationships between patient, physician, data, and knowledge. It enables a shift from a "reactive" medicine, centered on established disease, to a "proactive" medicine capable of anticipating, modulating, and preventing disease. The future of healthcare will depend on the ability to integrate these tools while respecting regulatory frameworks, human dignity, and the principle of equity. The role of educational institutions - such as **BRIA**-type training pathways - will be crucial in training a new generation of professionals who are knowledgeable, responsible, and capable of guiding this transformation with vision.

Table 5 lists currently approved AI models; many of these devices are classified as Software as a Medical Device (SaMD) and must comply with the **IEC 62304** (software life-cycle) standard, **ISO 14971** (risk management), **ISO 13485** (quality system), as well as the FDA guidelines "Total Product Lifecycle for AI/ML-based SaMD."

Table 5. Currently approved models

System Name	AI Type	Clinical Purpose	Company/Institution	Regulatory Status	Notes
IDx-DR	Deep Learning (CNN)	Automated screening for diabetic retinopathy	Digital Diagnostics (ex IDx)	FDA-approved (De Novo)	First AI algorithm authorized without final human review
Viz.AI LVO	Deep Learning + NLP	Early detection of large-vessel cerebral occlusion on CT	Viz.AI Inc.	FDA-approved, CE Mark	Automatic notification to stroke team within 3 minutes
HeartFlow FFR-CT	Model-based AI and computational fluid dynamic	Non-invasive functional assessment of coronary stenoses on CT	HeartFlow Inc.	FDA-approved, CE Mark	Uses personalized 3D models based on the patient's anatomy
Arterys CardioAI	Multimodal Deep Learning	Automated cardiac MRI and flow analysis	Arterys	FDA-approved, CE Mark	Cloud-native platform, interoperable with PACS
Paige Prostate	AI for histopathology (CNN)	Prostate cancer detection in biopsies	Paige.AI	FDA-approved (Breakthrough Device)	Trained on over 30,000 digital slides
Caption Guidance	Reinforcement Learning	Real-time support for cardiac ultrasound provided to non-expert operators	Caption Health	FDA-approved	Shows visual suggestions to optimize framing
DermaCompare	Computer Vision + predictive AI	Remote monitoring and screening of suspicious skin lesions	Emerald Medical Applications	CE approval (EMA)	Uses smartphone and a pre-trained neural network

6.2 Bioinformatics as the architecture of biomedical knowledge

Bioinformatics is now one of the key disciplines redefining medical and biological knowledge, representing the **cognitive and computational infrastructure** on which Precision Medicine is built. It arises at the intersection of computer science, molecular biology, statistics, and applied mathematics, and its main objective is to **extract structured, clinically usable knowledge** from complex, multidimensional, and highly variable biological data.

In an era marked by massive data production-ranging from **whole genomes** to **single cell transcriptomes**, from **epigenetic profiling** to **molecular imaging datasets-bioinformatics** is not merely a set of analytical techniques, but a true **knowledge architecture**, capable of building explanatory models of human biology and translating them into personalized clinical tools. It is at this interface that raw, disorganized data, such as DNA sequences or protein profiles converge and, through computational pipelines, are transformed into structured, **interpretable information suitable for diagnostic, therapeutic, or prognostic purposes.**

In Precision Medicine, the contribution of bioinformatics is central and manifests across several strategic, methodological, and technological levels, briefly described below.

1. Development of multi omic analysis pipelines. The construction of **automated, scalable, and reproducible workflows** for the integrated analysis of genomic, transcriptomic, epigenomic, proteomic, and metabolomic data constitutes one of the most relevant strategic challenges in contemporary bioinformatics and an **indispensable priority for Precision Medicine**. In a clinical context where each patient carries a biological complexity that cannot be reduced to a single molecular dimension, the ability to process multiple omic levels simultaneously and coherently is what enables the transition from simple molecular observation to **predictive modeling of individual disease**.

To manage these complex workflows efficiently and in a fully documented manner, the use of standardized computational languages and frameworks is essential. The **Common Workflow Language (CWL)** has emerged as an open, interoperable standard for the formal description of bioinformatics pipelines, enabling portability and reproducibility of analyses across laboratories, platforms, and computing environments. This is crucial to ensure **traceability, auditability, and inter institutional validation** of results, especially in clinical or regulatory settings. Alongside CWL, other computational platforms have emerged that represent the operational core of modern multi omic analysis laboratories.

Workflow standardization not only enhances the **reliability of analyses**, but also provides the infrastructural basis for building public repositories of validated pipelines that can be reused, updated, and certified at national or European level - for example, within infrastructures such as ELIXIR, GA4GH, or BRIA competence centers. Only through formalized and automated workflows will it be possible to develop scalable computational medicine applicable both to basic research and to hospital diagnostics.

In this sense, investing in the construction of integrated multi omic workflows means **building the operational grammar of Precision Medicine**: a shared, verifiable language through which raw biological data become actionable clinical knowledge. It also enables the **democratization of access to molecular innovation**, allowing even peripheral hospitals or institutions with limited resources to use the same advanced computational tools adopted in centers of excellence. Ultimately, it ensures that future medicine will not only be more precise, but also **more equitable, reproducible, and accessible to all.**

2. Construction of clinical biological semantic ontologies. To correlate, in a rigorous and computationally meaningful way, observable **clinical phenotypes-signs**, symptoms, disease manifestations, diagnostic test outcomes-with their **underlying molecular bases**, it is essential to adopt a structured, shared, and machine readable system for representing biomedical knowledge. This system takes the form of **computational ontologies**, i.e., formal sets of concepts and relationships that encode medical and biological knowledge in a format that can be processed by computer systems, artificial intelligence algorithms, and predictive models.

The use of **clinical biological ontologies** has both epistemological and technical significance. They act as a **semantic bridge** between the natural language used by healthcare professionals and the numerical codes required for automated processing. By adopting standardized ontological systems, it becomes possible to ensure interoperability between

heterogeneous IT platforms, integrate disparate data sources (EHRs, biobanks, IoT devices, omic datasets), and - above all - **automate clinical reasoning**, thereby enabling advanced decision support systems.

Among the main tools in this area, **SNOMED CT** (Systematized Nomenclature of Medicine - Clinical Terms) represents the largest existing clinical ontology, with over 350,000 hierarchically organized coded concepts used to map diagnoses, procedures, pathophysiological conditions, therapies, and clinical parameters. Its adoption supports not only the standard coding of medical data, but also semantic navigation across related concepts, which is useful for AI based inference and large scale predictive analyses.

Alongside SNOMED CT, the **LOINC** (Logical Observation Identifiers Names and Codes) system plays a fundamental role in coding clinical observations, laboratory results, and diagnostic measurements. Its granularity and semantic precision make it indispensable for interoperability between health information systems and for building integrated datasets used to train supervised learning models.

In the biological and molecular domain, the **Gene Ontology** (GO) is an essential standard for representing gene functions, biological processes, and cellular localization. GO enables hierarchical structuring of molecular information and the association of genes and proteins with defined functions, supporting enrichment analyses, semantic clustering, and functional prediction in contexts such as differential gene expression. Its application is crucial in bioinformatics workflows correlating transcriptomic profiles with clinical phenotypes.

Another key tool is the **Human Phenotype Ontology** (HPO), specifically designed to describe abnormal human phenotypes, especially in genetic and pediatric settings. HPO links clinical manifestations to candidate genes and rare syndromes, enabling phenotype based assisted diagnosis and semantic enrichment. AI systems that incorporate HPO can identify rare diseases starting from sets of signs and symptoms - addressing one of the most significant gaps in current medicine.

The synergistic adoption of these ontologies enables the construction of **knowledge graphs**, dynamic structures in which biomedical concepts are represented as nodes connected by semantic relationships. These graphs can be queried by machine learning algorithms to extract complex patterns, simulate causal relationships, identify biomarkers, or suggest personalized therapeutic options. In this way, clinical knowledge becomes not merely documented, but **computable, extensible, and adaptable to the context of the individual patient.**

The construction and maintenance of computational ontologies is not an accessory operation, but **a foundational requirement for the development of an AI driven Precision Medicine ecosystem**. Only through the shared formalization of clinical and biological knowledge can predictive models be accurate, explainable, interoperable, and truly integrable into daily clinical practice. In the architecture of computational medicine, ontologies represent the semantic foundations upon which every automatic clinical inference, every decision-support system, and every advanced diagnostic algorithm is built.

3. Data mining on clinical and biological big data. Through the application of **advanced statistical methods** and **machine learning algorithms**, modern bioinformatics has emerged as a true science of discovery in the biomedical field, capable of analyzing vast volumes of heterogeneous, high dimensional health data with the aim of **identifying clinically relevant biomarkers**. Once validated, these biomarkers become key elements for early diagnosis, prediction of therapeutic response, and assessment of short or long term prognosis.

Bioinformatics research focuses particularly on the ability to **extract meaningful patterns** from data derived from genomic sequencing, gene expression, protein profiles, hematobiochemical parameters, radiological images, biometric signals, and textual clinical annotations. In this context, **health data mining** is not simply a passive extraction of information, but an active process of algorithmic interrogation of biological data aimed at building **maps of clinical meaning**.

This process relies on a wide range of computational techniques **(random forests, penalized regression, Bayesian networks)** and **generative models** through which bioinformatics is now able to **detect previously invisible correlations** between complex molecular profiles and concrete clinical outcomes. This capability opens the way to a form of medicine based not only on clinical observation or theoretical knowledge, but on **robust, reproducible, and statistically significant computational evidence**. This paradigm is particularly valuable in the most critical clinical settings: **rare diseases**, where available data are scarce and scattered; highly heterogeneous tumors, where each patient represents

a unique case; **inherited metabolic diseases**, where the phenotype often results from complex gene-environment interactions; and **neurodegenerative disorders**, where early identification of molecular signs is crucial for effective intervention.

Worth mentioning is the integrated "*Network Medicine*" approach, which models the interactome through nodal structures and is widely used in the study of cardiovascular diseases, oncology, rare diseases, and organ transplant recipients, with the additional goal of optimizing immunosuppressive therapy [148-151].

The ability of bioinformatics to navigate large volumes of data using advanced algorithms is not merely a technical advantage - it constitutes an epistemological transformation. **I allows data to become knowledge, knowledge to become prediction, and prediction to translate into clinical action.** If conducted with methodological rigor and anchored to ethical and regulatory principles, this process represents one of the most promising cornerstones for the development of Precision Medicine in the coming decades.

4. Simulation and modeling of complex biological networks. The cell can no longer be viewed as a passive entity governed by linear, deterministic mechanisms, but must instead be understood as a **complex non-linear system** in which thousands of molecular components interact with dynamic relationships, feedback loops, and functional redundancies. In this context, understanding cellular behavior requires the ability **to model interactions between genes, proteins, metabolites, and intracellular signals**, while accounting for their stochastic nature, individual variability, and environmental influences. Bioinformatics, combined with systems biology, provides the computational tools needed to turn this complexity into predictive **models usable for clinical and therapeutic purpose**s.

Central to this approach are **biological interaction networks**, such as **gene regulatory networks (GRNs)** or **protein-protein interaction (PPI) networks**, which graphically and mathematically represent the functional connections between cellular components. Another fundamental pillar consists of **metabolic flux models**, which analyze the network of biochemical reactions underlying energy production, biosynthesis, and cellular detoxification.

Simulation of these networks is carried out through **dynamic and stochastic models** that consider not only the direct interactions between components, but also the intrinsic variability in biological processes, molecular noise, time dependence, and contextual conditions. These models allow **in silico testing** of the effects of a genetic variation, a targeted therapy, or an enzymatic manipulation, offering enormous advantages in terms of time, cost, and the ability to explore biological scenarios that would be experimentally infeasible in vivo or in vitro for ethical or technical reasons.

Such simulations will represent a turning point in **pharmacogenomics**, **oncologic Precision Medicine**, and **personalized prevention**, enabling the early identification of subjects with altered biological networks, even before the phenotypic expression of diseases.

The computational representation of the cell through interaction networks and their predictive simulation constitutes a **quiet yet profound revolution** in the understanding and treatment of diseases. It shifts medicine from treating symptoms to modeling underlying mechanisms, from reaction to prediction, and from generalization to personalization. These integrated, dynamic, and computational foundations form the basis upon which the new biology of healing is being built.

Beyond these priority areas, bioinformatics contributes to the **analysis of interindividual variability**, **re engineering clinical protocols**, and **designing personalized computational trials**, in which virtual cohorts can be simulated to accelerate the development and validation of new therapies. It is no coincidence that many platforms approved by EMA and FDA as SaMD are built on bioinformatic foundations, since "raw" data must first be structured, normalized, validated, and interpreted through computational models.

From a regulatory and normative standpoint, the use of bioinformatics in clinical settings must comply with strict standards of **data integrity, analysis traceability, model validation, and scientific reproducibility**, in line with European regulations such as **Regulation (EU) 2017/746 (IVDR)** for in vitro diagnostic tests and ISO standards including:

- **ISO 20387:2018** - quality requirements for biobanks providing raw biological material;
- **ISO/IEC 17025** - requirements for testing and calibration laboratories;
- **ISO 13485** - quality management for medical devices (including software);
- **FAIR Principles** (Findable, Accessible, Interoperable, Reusable) - for the management of omic data.

The **BRIA training program** fits perfectly within this scenario, developing professional profiles that combine molecular and genetic expertise with mastery of computational pipelines, thereby helping **bridge the gap between scientific discovery and clinical application**. Bioinformaticians trained to these standards are among the most sought after professionals internationally, as they can interface seamlessly with translational research and high level clinical practice.

Bioinformatics has become the **logical and computational brain** of Precision Medicine. It is not merely about analyzing data, but about giving **clinical meaning and strategic vision** to human biological complexity - transforming knowledge into care, and care into prediction. Those who master these tools do so not to replace the physician, but to **enhance their capacity** for understanding and intervention, always in respect of the persons and their biological uniqueness.

6.3 Predictive algorithms

Prediction constitutes the first logical and operational stage of Precision Medicine. The entire paradigm is based on the ability **to anticipate clinical events before they occur**, **model disease progression** in a personalized way, and **optimize therapeutic choices** according to individual biological characteristics. Unlike traditional medicine – which is oriented toward managing symptoms or manifest disease - predictive medicine relies on mathematical and statistical models capable of identifying weak signals in the data. Once interpreted, these signals can guide timely and targeted clinical decisions.

Predictive algorithms represent the quintessential computational tool of this approach. They are trained on large amounts of heterogeneous data: **historical information** (previous clinical outcomes, family history, lifestyles), **structured clinical data** (blood tests, imaging, electronic records), **omic data** (genomics, epigenomics, metabolomics), as well as **environmental and behavioral data**. Integrating these sources makes it possible to build dynamic, personalized, and continuously updatable models that adapt to individual clinical trajectories.

The main applications of predictive algorithms in Precision Medicine include:

1. Prediction of individual risk of developing a disease. The evolution of artificial intelligence applied to Precision Medicine has made it possible - through **advanced statistical models, neural networks**, and Bayesian probabilistic algorithms - to accurately estimate an **individual's lifetime risk of developing a disease**. This approach relies on integrating a wide range of personal data, including **genetic and epigenetic profiles**, **microbiome** composition, the socio-ecological environment, and the patient's entire past clinical and family history. Combining these factors into a single model enables a dynamic, updated, and personalized risk assessment, shifting medicine from a reactive framework to a fully predictive one.

One of the most emblematic and promising tools in this area is represented by **Polygenic Risk Scores (PRS)**. These are numerical indices obtained by summing the effects of hundreds or thousands of common genetic variants (single nucleotide polymorphisms, SNPs), each with a relatively small effect, but cumulatively capable of determining a significant genetic predisposition to a given disease. Research on the clinical application of PRS is rapidly expanding and now encompasses strategic areas of modern medicine. In **oncology**, for example, PRS are used to estimate the individual risk of developing hereditary cancers such as breast or prostate cancer, guiding decisions on intensified surveillance, early screening, or - in selected cases - prophylactic interventions. In **cardiology**, polygenic risk analysis helps predict the onset of coronary artery disease or atrial fibrillation, influencing therapeutic decisions even in young individuals, long before symptom onset. In **neurology**, for complex diseases such as Alzheimer's disease, PRS are emerging as complementary tools to imaging and biological-fluid analyses, contributing to the creation of integrated risk profiles.

The key advantage of these analyses is the possibility of **activating preventive measures before the disease manifests**. This includes personalizing screening schedules, anticipating diagnostic tests, modifying lifestyle behaviors, or, in the highest-risk cases, proposing pharmacological prevention. Moreover, these models can be continuously updated in real time as new clinical data and genomic knowledge become available, ensuring a predictive medicine that is **not static but adaptive**.

For these tools to be truly effective and reliable, however, they must be developed and validated on cohorts that are representative of the **genetic and environmental diversity** of the target population. A PRS calculated on data from European populations, for example, cannot be automatically applied to individuals of Asian or African ancestry without

generating significant predictive bias. This highlights the importance - also for Italy - of developing well-characterized, stratified **national datasets** capable of supporting **locally relevant**, equitable, and scientifically robust predictive models.

Estimating individual risk through sophisticated predictive models represents one of the most promising frontiers of personalized medicine. It allows not only identifying individuals at higher vulnerability, but also building **proactive clinical pathways** in which prevention is no longer generic, but **calibrated on the unique biological and environmental profile of each person**. A future in which every citizen can know their risk of disease, act to mitigate it, and receive personalized care before the pathology appears is no longer a utopian scenario, but a concrete developmental trajectory enabled by the convergence of genomics, artificial intelligence, and clinical responsibility.

2. Anticipation of therapeutic response. In the context of Precision Medicine, predictive models are fundamental not only for anticipating the onset of disease, but above all **for guiding therapeutic choices in a targeted and personalized way** - identifying for each patient the most effective molecule, the optimal dosage, and the safest administration regimen. This type of application, which falls within the sphere of **computational pharmacogenomics**, is crucial in therapeutically complex biological areas, particularly in **precision oncology**.

In clinical oncology practice, AI-based predictive models correlate a **tumor molecular profile**—obtained through techniques such as exome sequencing, transcriptomics, proteomics, and epigenetic analysis—with the probability of response to **molecular-targeted drugs**. These agents, known as targeted therapies, do not act broadly on rapidly proliferating cells, as traditional chemotherapy does, but **selectively target specific oncogenic mutations or deregulated signaling pathways** that characterize the tumor of a specific patient.

The effectiveness of this approach is enhanced by **deep-learning and supervised-learning algorithms** capable of identifying complex patterns within high-dimensional, intrinsically heterogeneous datasets, such as those derived from tumor samples. These models do not merely analyze the presence or absence of driver mutations; they integrate dynamic information from the tumor immunological context, the tissue microenvironment, systemic inflammatory response, and the patient's pharmacological history.

Thanks to these tools, it becomes possible to **computationally predict primary or acquired drug resistance** to certain drugs, i.e., the likelihood that a tumor, despite carrying the specific molecular target, will fail to respond to the drug due to compensatory mechanisms, alterations in downstream signaling pathways, or epigenetic modifications. Likewise, predictive models can **estimate individual drug toxicity** by considering genetic variations in genes involved in hepatic metabolism, cellular transport, or activation/inactivation of pharmacological compounds.

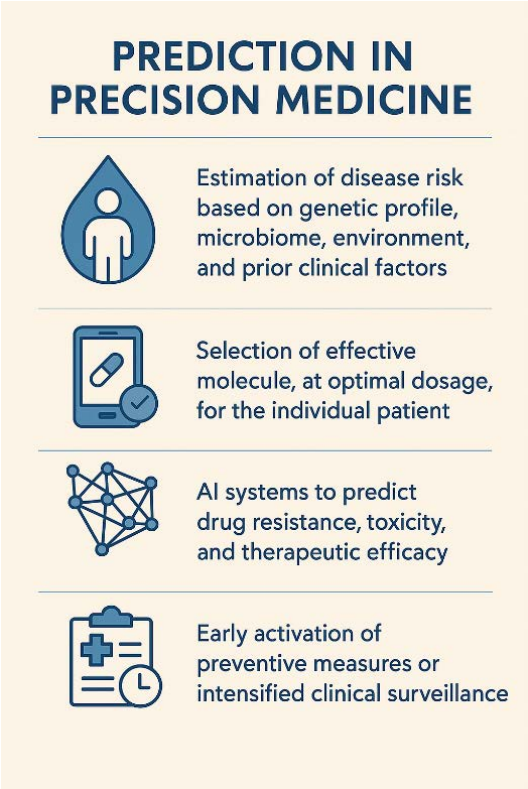
A further application lies in **determining optimal dosage**, which is no longer based on empirical, standardized parameters such as body weight or body surface area, but on individualized models that consider genetic polymorphisms, comorbidities, renal and hepatic function, and longitudinal clinical and laboratory data. Tailoring therapy in this way leads to a **significant reduction in side effects**, improved therapeutic adherence, and an increased probability of positive response.

In oncology, these models are already used to stratify patients eligible for anti-EGFR drugs, ALK, BRAF, PD-L1 inhibitors, and other targeted therapies. More advanced predictive systems - based on **multimodal architectures** integrating digital histopathology, genomic sequences, and clinical data - are showing the ability to anticipate treatment-response trajectories and suggest therapeutic adjustments before clinical or radiological signs of progression emerge.

It should be emphasized that, to be implemented in clinical practice, these models must undergo rigorous clinical and regulatory validation, in accordance with medical software regulations (MDR, IEC 62304) and AI transparency principles (explainability, accountability). However, if properly constructed and adopted, they represent **a transformational milestone in clinical pharmacology**, capable of moving medical prescribing from a statistical act to one that is computationally informed, molecularly targeted, and ethically responsible.

The integration of predictive models into personalized therapeutic selection **elevates care from a therapeutic event to a precision strategy** in which every choice is supported by data, simulations, and predictions tailored to the real patient - not to a statistical archetype. This represents the direction in which future medicine—more effective, safer, and more humane—must and can evolve.

3. Dynamic monitoring of disease progression. Predictive medicine is not an isolated action confined to the early stages of the care pathway, nor does it end with diagnosis or the selection of an initial therapy. Instead, it extends across the entire clinical course, functioning as a **continuous model of intelligent surveillance** capable of dynamically adapting to disease evolution and to the patient's biological responses. In this perspective, artificial intelligence acts as a sentinel system - a silent but constantly active observer that processes real-time clinical data **to anticipate critical events before they become clinically evident**.



Predictive models operate on **longitudinal data**, i.e., time-series information documenting the patient's condition over time. These data may include **daily monitored vital parameters** such as blood pressure, heart rate, blood glucose, and oxygenation; **sequential laboratory results** revealing subclinical variations in hematobiochemical biomarkers; **comparative diagnostic imaging** allowing detection of micro-morphological changes imperceptible to the human eye; **behavioral data**, such as therapy adherence captured through apps, wearable devices, or telemedicine platforms.

Through the integration of these data into evolutionary computational models—such as **recurrent neural networks (RNNs)**, **temporal Transformer models**, or **hidden Markov chains**—it becomes possible to generate dynamic predictions on **expected clinical evolution**, identifying in advance the risk of tumor recurrence, the **imminent re-exacerbation** of heart failure, or the onset of hypoglycemic crises or cognitive deteriorations in neurodegenerative patients. These predictions are not simple statistical extrapolations but **adaptive simulations** that learn from individual trajectories and compare each new datum with models of similar patients in comparable clinical contexts.

This approach finds one of its most effective applications in the **management of chronic diseases**, an area of medicine that is particularly burdensome for both patients and healthcare systems. Conditions such as type 2 diabetes mellitus, chronic heart failure, COPD, or neurodegenerative diseases like Alzheimer's and Parkinson's are characterized by a prolonged, variable, and often unpredictable course, with phases of apparent stability that can rapidly degenerate into critical conditions. In these cases, **anticipating clinical worsening even by just a few days** can make the difference between outpatient management and emergency hospitalization, between preventing a complication and intervening too late.

Longitudinal predictive medicine enables **proactive intervention**: activating alert mechanisms, adapting therapy, or intensifying monitoring before the patient crosses critical clinical thresholds. This not only improves the patient's quality of life - reducing anxiety, pain, and disease unpredictability - but also generates a positive systemic impact: reduced hospitalizations, improved continuity of care, reduced use of high-intensity resources, and a sustainable transition toward **predictive local and home-based care models**.

In prospect, temporal predictive models will be integrated directly into physicians' decision-support systems, generating **contextualized clinical alerts**, suggesting pharmacological interventions, or adapting the care plan based on detected weak signals. The BRIA technological infrastructure, with its integration of clinical data, bioinformatics, and immersive reality, can provide the foundation for **advanced predictive-simulation environments**, where physicians and patients can explore in real time the expected evolution of disease and make shared decisions based on personalized and explainable models.

Predictive medicine that accompanies the patient throughout the entire clinical course is not a digital accessory but a **new paradigm of intelligent care**, in which time is no longer an enemy to chase but a resource to govern. It transforms the management of a chronic disease from a sequence of emergencies into a **continuous strategy of prediction, adaptation, and protection**.

4. Simulation of virtual trials (in silico). Through the use of **advanced computational models**, contemporary biomedical research now has the concrete possibility to **simulate virtual patient cohorts**, built on molecular, clinical, and pathophysiological bases, in order to test the **efficacy and safety of new therapies** before they are experimented on human beings. This approach, known as in silico clinical trials, represents one of the most extraordinary innovations in computational medicine and is rapidly evolving from an experimental tool to an **emerging standard in preclinical regulatory evaluation**.

The underlying principle of this method consists in the **creation of digital twins**, i.e., dynamic and adaptive computational representations of real or potential patients, built on biological, clinical, genetic, environmental, and behavioral data. These digital twins are not simple static avatars but **evolutionary models** capable of responding to pharmacological stimuli, biological mutations, environmental or physiological variations, according to simulated rules based on **causal networks**, differential equations, probabilistic generative models, and agent-based modeling. In other words, they are systems that **"live"** and react in a realistic and predictive manner, allowing scientists to observe in advance the impact of a therapeutic intervention as if administered to a real patient, but in a controlled digital environment.

One of the distinctive elements of this technology is the ability to build **heterogeneous virtual cohorts**, including patients with multiple comorbidities, rare genetic conditions, or belonging to groups underrepresented in traditional trials, such as children, frail elderly, pregnant women, or immunocompromised subjects. This extraordinarily expands the exploratory capacity of clinical trials, reducing **selection bias** and increasing the generalizability of the generated evidence. Moreover, in silico models allow evaluation of **interactions between multiple variables** (e.g., dosage, administration timing, polytherapies) with a granularity and precision that are difficult to replicate in real-world contexts, both for practical limitations and ethical reasons.

The systemic impact of this approach is potentially revolutionary. On one hand, it enables a **significant reduction in the costs and time** required to bring a new therapy from the preclinical phase to phase I/II trials. Some in silico simulations, in use at pharmaceutical companies or international academic consortia, have demonstrated the possibility of saving 30-40% of the initial experimental budget. On the other hand, it contributes to **minimizing ethical risks**, as many variables can be tested and discarded in a virtual environment before exposing real subjects to potential adverse effects. This is particularly important in the contexts of **rare diseases or gene therapies**, where patient availability is limited and every error can have irreversible consequences.

The reliability of such simulations is no longer a mere academic hypothesis. The concept of **regulatory-grade modeling** is already at an advanced stage of adoption by major international regulatory agencies. The U.S. Food and Drug Administration (**FDA**), for example, has launched a series of initiatives to integrate in silico models into accelerated approval pathways, particularly in the areas of pharmacokinetics, drug-drug interactions, and personalized therapies. The European Medicines Agency (**EMA**), on the other side, has included predictive computational models in the context of the *Adaptive Pathways Strategy*, envisaging their applicability as complementary tools in regulatory dossiers. Furthermore, organizations such as the **Society for Simulation in Healthcare and the Virtual Physiological Human Institute** are working on shared guidelines for the validation and certification of these models for regulatory purposes.

The prospect that opens up is one of **integrated pharmacological experimentation**, in which traditional phases (in vitro, in vivo, clinical) are accompanied by an autonomous, robust, and legally recognized computational phase, with documented and traceable predictive value. This paradigm, beyond accelerating therapeutic innovation, offers a decisive contribution to **Small Number Medicine**, opening new therapeutic possibilities for patients hitherto excluded from conventional development pathways.

In silico simulations are not a technology of the future but a reality that is already becoming established, which enables **imagining, testing, and optimizing treatments in a virtual laboratory** before safely bringing them to clinical testing (see Appendix 1 "*Example of in silico simulation*"). In an era where every day of delay in experimentation can translate into lives lost and public resources must be invested with rigor and transparency, computational predictive modeling presents itself as a **new ethics of experimentation**, capable of combining science, efficiency, and responsibility.

Predictive algorithms used in precision medicine (see table 6 and Appendix 2 "*Algorithmic architecture of clinical prediction*") are distinguished not only by their mathematical architecture but also by the function they perform in the

clinical decision-making process, by the nature of the data on the basis of which they operate, and by the degree of **interpretability** they offer—an element which is crucial especially in the healthcare field, where every decision must be justifiable, communicable, and traceable.

The appropriateness of the algorithm is measured not only in terms of statistical accuracy but also depending on its **ability to adapt to clinical contexts**, to generate trust among healthcare professionals, and to comply with regulatory and normative requirements.

Prediction in precision medicine is not an accessory phase but the **gateway to a new paradigm of care**. Through sophisticated and rigorously validated algorithmic tools, it is possible to transform data into proactive, personalized, and effective medical actions. In this regard, training new specialists capable of designing, training, interpreting, and validating these models—as envisaged in the BRIA programs—is not only desirable but absolutely essential for the near future of healthcare.

Table 6. Main predictive models in precision medicine and their clinical applications

Algorithm	Type	Main Function	Clinical Applications	Notes
Random Forests	Ensemble Learning	Robust classification and noise management	Cardiovascular risk, oncological staging, prediction of post-operative adverse events	Good interpretability of variables
Gradient Boosting Machines (GBM, XGBoost)	Boosting Ensemble	Prediction optimization, high performance	Prediction of drug resistance, therapeutic response in oncology, sepsis prediction	Competitive model in supervised contexts
Recurrent Neural Networks (RNN, LSTM)	Deep Learning for sequences	Temporal data modeling	Real-time monitoring of critically ill patients, ECG/EEG analysis, and glycemic trend monitoring in diabetic patients	Excellent for sequential data but require large amounts of data.
Transformer (e.g. Med-BERT, GatorTron)	NLP & Deep Learning	Semantic and temporal understanding from text and time series	Automatic extraction from clinical records, outcome prediction, and emergency triage	New standard in clinical foundation models
Bayesian Networks	Probabilistic	Modeling dependencies among clinical variables	Decision support system, personalized predictive assessment, diagnostic scenario simulation	Strong explanatory power and transparency
Generative Adversarial Networks (GANs)	Generative Modeling	Realistic simulation of clinical data or images	Virtual trials, generation of synthetic MRI/CT images, in silico models for rare patients	Useful for increasing data in rare diseases or in conditions that are costly to analyze
Polygenic Risk Score (PRS)	Statistical genetics	Cumulative risk calculation based on genomic data	Risk of developing hereditary cancers, Alzheimer's disease, and cardiovascular diseases	Based on GWAS and common genetic variants

6.4 The need to create an Italian predictive model

To create a predictive model in Italy that is truly superior to those currently in use and cited in major international experiences, it is not enough to simply replicate existing technologies or adopt solutions imported from other healthcare systems. On the contrary, it is necessary to develop a national infrastructure that integrates excellence in biomedical research, bioinformatics, and artificial intelligence with the healthcare and clinical heritage of our country, within a design process that combines strategic vision, computational capacity, ethical governance, and continuous training. A project of this nature, if built according to the principles of the BRIA discipline, could position Italy as a European reference model in the field of predictive and personalized medicine.

Such a model should be developed within a national predictive medicine platform, built on a broad, interdisciplinary alliance involving Scientific Institutes for Research, Hospitalization and Healthcare (IRCCS institutes), university hospitals, research centers such as the National Research Council (CNR) and the National Agency for New Technologies, Energy and Sustainable Economic Development (ENEA), universities and polytechnics, high-tech companies active in bioinformatics and AI, regulatory bodies such as the Ministry of Health, the Italian Medicines Agency (AIFA), and the Italian National Agency for Regional Healthcare Services (AGENAS), as well as patient organizations and scientifically engaged citizens. The platform should be structured into interoperable regional hubs, collaborating under the coordination of a national center. The main task of this network would be to collect and harmonize clinical, molecular, genomic, radiological, and behavioral data from different sources, making them available in de-identified and structured form for the training of predictive models, in full compliance with European data-protection regulations (GDPR) and in adherence with FAIR principles, which require data to be findable, accessible, interoperable, and reusable.

Data quality is a crucial point: even the most sophisticated algorithm fails if predicated on substandard data. For this reason, the development of a national predictive model should be based on the creation of a large unified archive, an Italian “National Health Dataset,” derived from the integration and normalization of regional information flows, which are currently fragmented. These data, which would include historical information, longitudinal data from electronic health records as well asomics and environmental data, should be restructured using a multimodal and multitemporal approach, according to shared technical standards such as HL7 FHIR, SNOMED CT, and ICD-11. Italy already has an extensive healthcare network and a massive volume of potential data: the challenge lies not in collecting these data, but in harmonizing them and making them suitable for transparent and reproducible decision-making models.

The core of this initiative will be represented by a next-generation adaptive algorithm, developed to be not only technically advanced, but also ethically sustainable, energy-efficient, and clinically explainable. To outperform existing models, the Italian model should have the capability to update dynamically by integrating real-world evidence, to provide clear and comprehensible rationales for each prediction, and to autonomously monitor potential distortions arising from ethnic, gender, or geographic biases. Moreover, it must be able to process heterogeneous data sources simultaneously and in an integrated manner, combining medical texts, radiological images, genetic profiles, and physiological signals. The entire system, from its initial design phase, must comply with the evolving European regulatory framework (in particular the AI Act), the medical-device regulation, and the principles imposed by privacy legislation.

A key element that would deeply distinguish the Italian model is the native integration into advanced simulation environments based on immersive reality, as envisaged in the BRIA paradigm. Through interactive 3D environments, it will be possible to test the predictive model in realistic and dynamic clinical scenarios, verifying its performance, simulating interaction with healthcare staff, and measuring its impact on therapeutic decisions and resource allocation. These environments will serve not only for technical validation, but also as training platforms for physicians, researchers, and students, enabling the dissemination of predictive-medicine culture in an experiential and accessible way.

The development of such a model would require planning in three phases. In the first phase, to be completed within six to nine months, a comprehensive mapping of data sources should be carried out, institutional agreements signed, a national ethical protocol defined, and the harmonization process initiated. In the second phase, lasting about nine to twelve months, the computational architecture of the algorithm should be built, the first models should be trained on pilot cohorts, and an iterative tuning and validation phase conducted. Finally, over an additional six to eight months period, the system should be certified as medical software (if necessary), integrated into selected healthcare facilities, a dedicated training package developed, and the results and potential of the project publicly disseminated. In total, a

project of this scale could be finalized in approximately twenty-four to thirty months, with the involvement of hundreds of stakeholders and a clear, public, and transparent governance model.

The benefits that would derive for the NHS are enormous. In terms of efficiency and sustainability, an Italian predictive model would significantly reduce inappropriate hospitalizations, improve the allocation of healthcare resources, and decrease pharmaceutical spending thanks to targeted treatment selection. From a clinical standpoint, it would increase diagnostic accuracy, anticipate adverse events, and improve patients' quality of life through personalized, dynamically adaptive care pathways. At the system level, it would mean having a sovereign infrastructure, designed and controlled at national level, free from the commercial logic of big tech companies and oriented towards public health. Finally, it would represent an extraordinary opportunity for growth in the BRIA-technology supply chain, creating new professional profiles, encouraging ethical innovation, and positioning Italy as a European leader in the application of artificial intelligence to medicine.

In short, the development of a national Italian predictive model, grounded in BRIA principles, represents not only a technological and healthcare opportunity, but also an act of strategic vision, political responsibility, and social justice. Acting now means securing for our country a future in which care is truly anticipated, intelligent, and human.

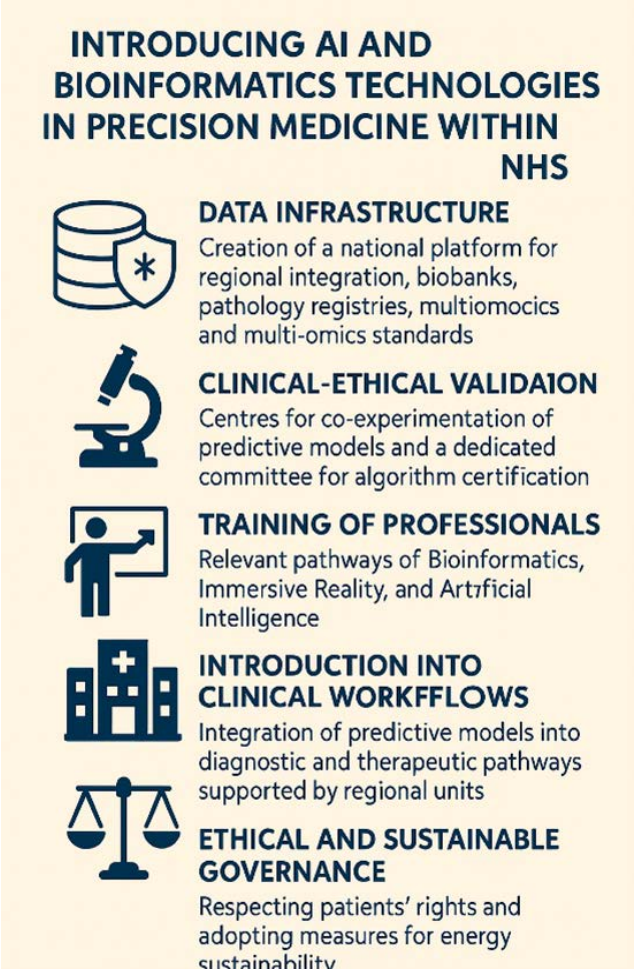
The systematic introduction of Artificial Intelligence and Bioinformatics technologies into precision medicine within the Italian NHS represents not only an urgent necessity dictated by the evolution of contemporary medicine, but also an extraordinary historical opportunity to rethink the entire structure of public healthcare. Precision medicine, based on a molecular, predictive, preventive, and personalized vision of care, can be fully achieved only through deep integration between clinical expertise and computational capabilities. It is therefore time to define a national operational model that, by overcoming fragmentation and episodic experimentation, gives shape to a coherent, efficient, and humanly sustainable ecosystem.

The first strategic issue to address is the construction of a unified, reliable, and interoperable infrastructure for managing healthcare data. In Italy, valuable biological and clinical archives already exist, albeit currently in scattered form, originating from IRCCS institutes, local health authorities (ASL), university hospitals, biobanks, and disease registries. However, there is still no system in place to make them interoperable, comparable, and capable of real time updates. It is necessary to create a national data platform for predictive medicine, built around principles of privacy by design and structural security, inspired by GDPR and NIS2 guidelines, capable of guaranteeing anonymization and ethical oversight in data use. This platform shall include a central hub for data quality assurance—a sort of "National Certification Center for Biomedical Data"—entrusted with ensuring semantic standardization (through SNOMED CT, LOINC, HL7 FHIR), checking completeness and correctness, and conducting periodic audits of datasets used by public institutions and researchers. Only on this basis will it be possible to build clinically reliable predictive models.

Alongside the infrastructure, it is essential to establish an institutional mechanism for the scientific, clinical, and ethical validation of algorithmic solutions. Many AI models, despite being sophisticated, remain confined to research laboratories or academic papers, without real-world testing. It is therefore necessary to set up national hubs for clinical and computational co-experimentation, preferably located in IRCCS centers and university-oriented hospitals. In these hubs, the experimental model should be based on adaptive trials, in silico simulations, patient digital twins, causal networks, and generative models. Computational technologies must be validated on real cases, with active involvement of physicians, pharmacologists, pharmacists, and other specialists who will ultimately use them. The data generated by these studies should also be shared with a regulatory oversight body: a National Committee for Computational Ethics and Predictive Medicine, capable of providing integrated assessments of clinical effectiveness, algorithmic risk, energy impact, and decision transparency. This Committee should work with AGENAS, the Istituto Superiore di Sanità (ISS), the Medical Association, and the Data Protection Authority to build a regulatory framework that is both innovative and protective of patients' rights.

Crucial in this process is the human dimension. No predictive model will ever be truly effective if its users—physicians, biologists, nurses, pharmacists—are not able to understand it, evaluate it, and adapt it to individual clinical cases. For this reason, the plan must include, from the very beginning, a systematic investment in training. The BRIA pathways—acronym for Bioinformatics, Immersive Reality, and Artificial Intelligence—represent the strategic key to training hybrid professionals capable of moving between the clinical and the algorithmic worlds, understanding the meaning of automated decisions, interrogating models, and recognizing their limits. These pathways should become an integral

part of university curricula in Medicine, Biology, Biotechnology, and Biomedical Engineering, as well as in ITS courses, postgraduate master's programs, and mandatory ECM (Continuing Medical Education) credits. Incentives should also be provided for young people choosing these paths—scholarships, training-and-employment contracts, access to industrial doctorates—as well as a national BRIA skills certification system, valid in both public and private sectors. The citizen-patient must also be involved, through digital-literacy campaigns, transparent platforms, and narrative interfaces that return to the individual conscious control over their own data and decisions.



Operational integration into real clinical workflows represents the most delicate and decisive phase of the process. Predictive models must not remain external to the system, but shall become part of diagnostic-therapeutic pathways, electronic health-record systems, and ward-level decision-making processes. In oncology, cardiology, metabolic diseases, and neurology, "digital twins" of patients can be created—dynamically updated computational representations that enable therapeutic simulations, risk assessments, and continuous care adjustments. This does not mean automating medicine, but enriching it: providing physicians with additional tools to navigate the growing complexity of clinical data. To achieve this, it will be essential to establish "clinical BRIA units" in every region—multidisciplinary teams capable of supporting the introduction of predictive medicine, performing algorithmic audits, training colleagues, and ensuring correct use of the technologies.

Finally, all of this must rest on a principle of ethical and sustainable governance. For an algorithm to enter public medicine, it must adhere to certain fundamental principles: non- discrimination, avoiding unsustainable consumption of resources, and strengthening - rather than replacing - the doctor-patient relationship. Mechanisms for environmental assessments of the code, green certifications for healthcare software, and energy audits of algorithms used in public centers must be introduced. The Assisi Theorem, which allows calculation of the computational weight and ecological footprint of every bit produced, could become the European standard for ensuring digitally efficient yet ecologically lean medicine. In parallel, the rights of the digital patient must be guaranteed: the right to understand, to be informed, to refuse an algorithmic decision, and to request explanations. All these rights should be codified in a new statute of the person within the predictive healthcare system.

If implemented with courage and method, such a plan would not only make the Italian healthcare system more modern and efficient, but would also restore it to its original foundation: caring for the person with all the tools of science, knowledge, and justice. Predictive medicine is not just a technological revolution. It is a choice of civilization.

Phase	Main objective	Strategic actions	Involved actors	Estimated timelines
Data infrastructure construction	Create an interoperable ecosystem of multi-omic and clinical healthcare data	- National platform for clinical and biological data - Semantic standardization (SNOMED CT, HL7 FHIR, LOINC) - National center for data quality	Ministry of Health, ISS, IRCCS, ASL, Data Protection Authority	Year 1–2
Scientific and regulatory validation	Testing, certifying, and integrating predictive models in real clinical environments	- Digital trials and *in silico* simulations - National committee for AI certification - Collaboration with EMA/FDA for regulatory-grade modeling	IRCCS, Universities, AIFA, Agenas, Ministry of Health	Year 2–4
BRIA training and profiles	Create new hybrid professional roles and upskill healthcare staff.	- National accreditation of BRIA pathways - Integration into university and ITS courses - ECM training and patient literacy/health literacy	MIUR, Universities, Higher Technical Institutes, Professional Orders	Year 3–5
Integration into clinical workflows	Implement predictive models in hospital wards, local health authorities (ASL), and territorial medicine	- Integration into digital care pathways (PDTA) - Digital twins in oncology, cardiology and geriatrics wards - Regional BRIA task forces	Regions, Hospital Trusts, ASL, Doctors	Year 4–6
Ethical and ecological governance	Ensure transparency, sustainability, equity, and respect for patients' digital rights	Assisi Theorem for computational efficiency Charter of digital patient rights National deontological code for AI in healthcare	FNOMCeO, Ministry of the Environment, Data Protection Authority, CNB	Year 5–7

6.5 Research priorities for the future

In the current context of precision medicine, where the integration of Artificial Intelligence and bioinformatics has reached a level of technological maturity sufficient to support complex clinical applications, it is necessary to clearly outline **future research priorities** to ensure that innovation is not merely experimental or marginal, but truly transformative of the entire healthcare ecosystem. These priorities are not mere theoretical goals, but indispensable pillars for building a predictive, personalized and truly accessible medical system, capable of improving public health, ensuring equity, and the sustainable implementation of emerging technologies.

The first major priority concerns **the construction of harmonized, interoperable and shared datasets**. The predictive performance of an algorithm directly depends on the quality and representativeness of the data on which it is trained. Too often, clinical models are based on small, ethnically and geographically limited samples, collected under non-standardized and non-updatable conditions. Instead, a coordinated effort is required at national and European level to generate **dynamic clinical biobanks**, in which data are collected ethically, anonymized in compliance with the GDPR, and structured according to common standards (such as HL7 FHIR for the clinical component, or OMOP CDM for health data). These datasets must fairly and proportionally represent all human variables: sex, age, ethnicity, socioeconomic status, multiple comorbidities, and rare conditions. Without this shared knowledge infrastructure, artificial intelligence in medicine risks becoming an elitist technology, valid only for a few patients and in highly specialized settings.

A second crucial theme is **transparency and explainability of AI models**, also known as XAI (eXplainable Artificial Intelligence). For a predictive system to be adopted in clinical workflows, it is essential that clinicians understand which **variables the prediction is based on** and with what degree of confidence. Likewise, patients must be able to know why a certain therapy has been recommended and what it implies in terms of risk and benefit. Without explainability, there

is no trust; and without trust, there is no clinical adoption. Models will therefore need to incorporate interpretive structures (such as LIME, SHAP, attention maps, or intrinsically interpretable models) and intuitive visualizations, with clinical interfaces validated in real-world settings. The goal is not to oversimplify AI, but **to make it communicable, auditable and compatible with medical deontology**.

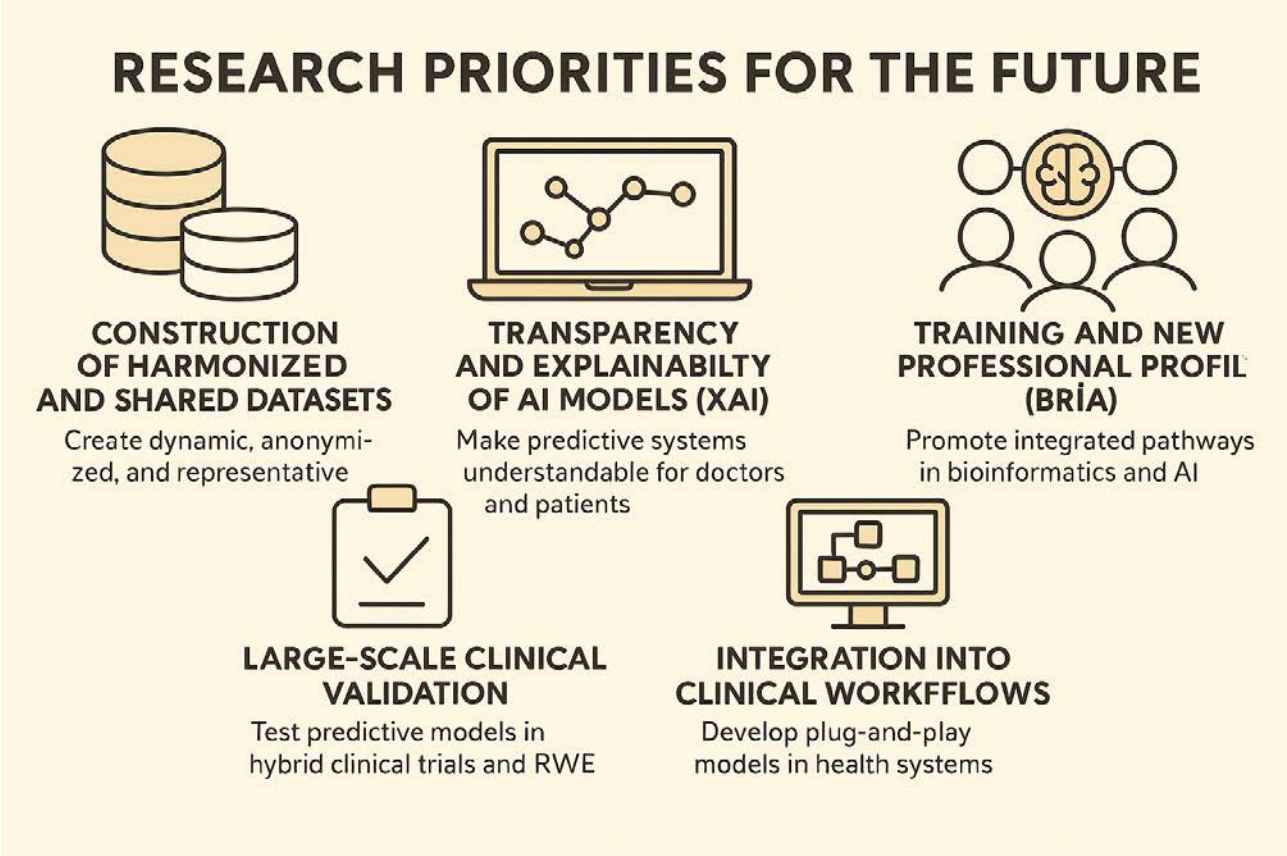
The third priority focuses on **large-scale clinical validation**. Too many AI algorithms remain confined to university laboratories or scientific publications, never facing the test of the real world. Future research must shift toward **hybrid trials**, in which models are tested on extended cohorts of patients in genuine clinical environments, monitoring not only algorithmic performance, but also the real impact on patient outcomes, diagnosis times, therapeutic compliance and cost sustainability. In this sense, the "real-world evidence" (RWE) approach should be regarded as an extended form of clinical experimentation, where data collected in real healthcare settings become the basis for improving the models themselves. Validation should not be an endpoint, but a **continuous process of feedback and updating**.

A further line of action concerns **integration into hospital clinical workflows**. A good algorithm, in order to be useful, must be incorporable into health information systems without radically changing existing processes, but enriching them. Research should therefore focus on creating **plug-and-play** models, capable of interfacing with electronic health record software, operating in the background with automatic updates, and providing contextual, non-intrusive decision support. Friction between technology and clinical practice should be minimized through ergonomic interfaces, standardized APIs, common languages and semantic interoperability.

The fifth major pillar is training and the **creation of new professional profiles** capable of operating at this new frontier of medicine. Traditional roles –physician, biologist, engineer, computer scientist – alone are not enough. A new generation of **hybrid** professionals is required, who understand molecular biology, can analyze omics data, grasp machine-learning algorithms, and are able to translate all this into clinical decisions. **BRIA** pathways, built on the integration of Bioinformatics, Immersive Reality and Artificial Intelligence, provide the ideal educational framework for training these new experts. Widely disseminating such pathways in universities, ITS academies and specialist schools is an investment not only in human capital, but also in the very **resilience of the healthcare system**.

Finally, every scientific advancement must be accompanied by an **ethical and ecological governance of AI**. It is necessary that every clinical algorithm be developed in respect of fundamental values: equitable access, non-discrimination, protection of personal data, and, above all, **energy sustainability**. The computational consumption of AI models – especially those based on deep learning – is not neutral. In this area, Italy can distinguish itself by adopting, from the outset, principles of energy-aware design, such as those envisaged in the Assisi Theorem, which evaluates the physical, energy and environmental cost of digital computation. Responsible predictive medicine is not only that which anticipates disease, but that which **respects life, the planet and social justice**.

Research priorities for AI and bioinformatics in precision medicine must aim not only at technological power, but at their real **embedding in the care system**, in everyday practice and in patients' lives. Only in this way will innovation be not only effective, but also human, fair and durable.



6.6 Training Pathways: the key to supporting the precision medicine ecosystem

The evolution of technologies in precision medicine – integrating computational biology, artificial intelligence, omics analysis and immersive simulation – has generated a training gap of worrying dimensions. Traditional universities struggle to update their curricula with sufficient speed, while healthcare institutions face growing difficulties in finding qualified personnel able to understand and implement advanced technological solutions in real clinical settings. In response to this systemic need, interdisciplinary training pathways such as **BRIA** (Bioinformatics, Immersive Reality, Artificial Intelligence) are emerging, configuring themselves as the new frontier of health and scientific education.

The BRIA paradigm: vertical and integrated training

The BRIA pathway was created to bridge the gap between computational research, clinical practice and the management of emerging technologies. It is a modular and progressive educational model, capable of guiding students – whether recent graduates, healthcare professionals, or IT technicians – from an understanding of theoretical foundations to the ability to design, apply and evaluate intelligent systems in medicine.

The verticality of BRIA includes at least three main axes:

- **Clinical bioinformatics:** training on algorithms for genomic analysis, protein structures, molecular models and simulation of metabolic pathways.
- **Immersive reality and simulation:** use of 3D environments for medical training (surgical simulation, virtual rehabilitation environments, interactive molecular visualization).
- **Artificial Intelligence in medicine:** development and application of predictive algorithms, machine learning, natural language processing for decision support and disease prediction.

All of this is framed within a methodological structure that prioritizes experiential learning, real projects (co-worked with clinics and companies) and a strong orientation towards employability.

The value of BRIA for the healthcare and industrial system

BRIA pathways are currently supported by networks of enterprises, research foundations and higher technical institutes (ITS) operating in synergy with public bodies, universities and hospitals. In Italy, in particular, the **Fondazione Olivetti Tecnologia e Ricerca Olitec** is one of the main promoters of these pathways, recognizing in BRIA a concrete and sustainable response to the crisis of technical-scientific personnel in the healthcare sector.

The advantage of BRIA pathways lies in their **immediate professional applicability**. Participants acquire certified skills in the fastest-growing employment sectors: analysis of health data, AI-based diagnostic support, management of advanced clinical simulation, medical software design , bioinformatic validation. This makes it possible not only to train new hybrid professional figures – such as the clinical bioinformatician, the healthcare immersive-reality technician, or the computational-risk analyst – but also **to ensure qualified and stable employment**, as already demonstrated in dozens of concrete cases in the Italian regions where the BRIA has been implemented.

Training grounded in ethics, sustainability and impact

Finally, the BRIA pathway is not limited to providing technical tools. It is based on an ethical vision of technology and on the urgency of adopting sustainable solutions also in the digital domain, in line with the principles of the Assisi Theorem, which evaluates the energy and environmental impact of computational processing. BRIA training therefore includes modules on:

- governance of Artificial Intelligence,
- protection of biometric and genomic data,
- the right to understanding and accessibility of healthcare technologies,
- respect for human dignity in experimentation and in the personalization of care.

Appendix 1. Example of in silico simulation

In the context of a public healthcare system increasingly oriented towards prevention and personalized care, an in silico simulation represents a concrete opportunity to illustrate how the introduction of BRIA technologies can transform the paradigm of precision medicine within the NHS. Imagine, therefore, a pilot project developed in an Italian Region with one million inhabitants, where three Local Health Authorities (ASL) decide to integrate an AI-based predictive system into their territorial medicine services, with the specific aim of anticipating serious cardiovascular events in patients at medium-to-high risk.

The cohort selected for the simulation consists of ten thousand citizens, aged between fifty and seventy-five years, already monitored for conditions such as hypertension, hypercholesterolemia or family history of cardiovascular events. All subjects are profiled through an aggregation of traditional clinical data, genomic data, laboratory parameters, environmental and behavioral indicators. The collected data include values such as blood pressure, blood glucose, renal function and cholesterol levels, but also molecular information such as the presence of genetic variants associated with ischemic risk, as well as elements derived from the territorial context, such as exposure to pollutants or social vulnerability. All this information is harmonized and structured according to standards of interoperability and traceability, making it usable within a machine-learning predictive engine.

For each patient a digital twin is created: a dynamically updated computational representation that integrates causal models and recurrent algorithms capable of learning from time-series clinical data. The system, fed by a training base composed of hundreds of thousands of clinical records already archived at national level, produces a personalized prediction of the risk of major ischemic event within the next thirty-six months. The result of this analysis is displayed within the electronic health record system used by general practitioners, with an interface that explicitly shows the estimated risk value and the factors that determine it, supported by automatic explanations provided through XAI modules.

In the case of a sixty-six-year-old patient with hypertension and a history of smoking, who presents a genetic variant associated with cardiovascular risk and a slightly elevated C-reactive protein, the system estimates an individual risk of thirty-two percent of experiencing an ischemic event within the next three years. At this point the physician can access, through an integrated module, an in silico simulation that allows different intervention scenarios to be tested. In the scenario of no change in the therapeutic plan, the risk remains unchanged; the introduction of a statin combined with lifestyle modifications reduces the risk to twelve percent; a more intensive strategy, including polytherapy and access to a cardiovascular rehabilitation program, brings the residual risk below six percent.

The physician shares these data with the patient in visual form, either through an immersive representation or through a traditional interface, making the available alternatives understandable. The patient is thus involved in the decision-making process, signs informed consent for predictive personalization, and embarks on an intensive monitoring pathway. Over the following twenty-four months, the patient's clinical parameters are automatically collected via integrated devices, continuously updating the digital twin and generating new predictions at every significant change in health status. Each deterioration is detected weeks in advance, allowing proactive intervention before clinical damage becomes evident.

The overall results of the simulation show a significant reduction in expected cardiovascular events within the analyzed population, with a positive impact both in terms of public health and in economic terms. The avoided events produce an average saving of almost two thousand euros per patient, while therapeutic adherence improves markedly in subjects followed via digital twin. At the same time, the entire workflow is documented and validated, providing scientific evidence useful for supporting the generalization of the model to other Italian Regions or to other disease areas.

This in silico simulation demonstrates not only the technical feasibility of predictive medicine integrated into the SSN, but also the transformative potential of combining real data, generative models and clinical decision processes. It is not simply a matter of increasing diagnostic precision, but of reconfiguring the relationship between medicine and time: shifting from treating the disease once it manifests, to predicting, preventing and protecting before it appears. Simulation of the future, if conducted in a rigorous, transparent and shared manner, is no longer merely a theoretical exercise, but a new dimension of care

Simulated baseline situation

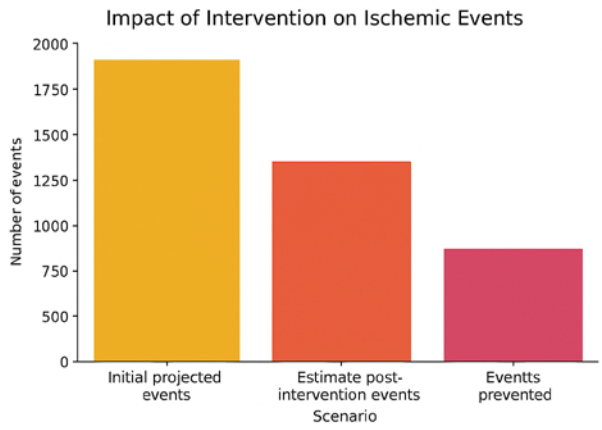
The simulated experiment that led to the integration of predictive models based on BRIA technologies into precision medicine within the NHS stems from a specific epidemiological and structural need. Italy, like many European countries, faces a double burden of disease: on one hand, population ageing, with a progressive increase in chronic conditions (cardiovascular diseases, diabetes, cancer, neurodegenerative diseases); on the other, growing availability of health data – clinical, genomic, environmental – which, if not organized, analyzed and systematically exploited, risk remaining an untapped potential.

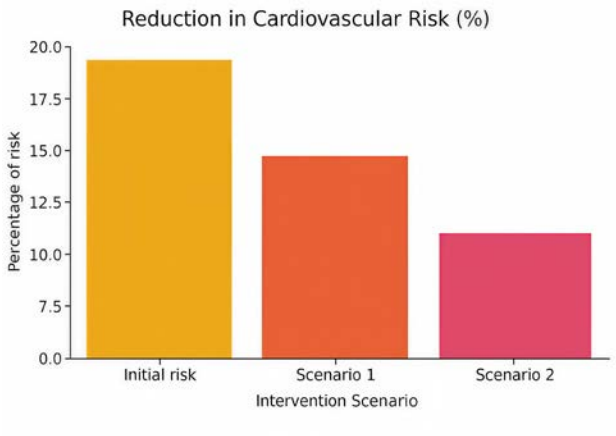
The starting point of the simulation is the aggregation of a longitudinal dataset obtained from a reference Italian Region, with a target population of about 1,000,000 inhabitants. Of these, 10,000 subjects were selected as a representative cohort according to demographic, clinical and genetic characteristics, in particular individuals aged between 50 and 75 years affected by at least one documented cardiovascular risk factor (hypertension, dyslipidaemia, previous ischemic event, family history, active smoking, obesity or sedentary lifestyle).

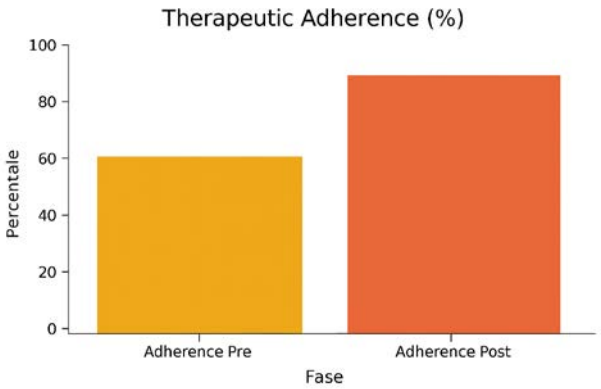
The starting data include electronic health records (CUP and diagnostic reports), laboratory tests, pharmacological data, radiological images and omics data from analyses performed on a subgroup of 1,500 patients (including DNA sequencing, epigenetic and transcriptomic profiles, microbiome data and blood metabolites). These data were integrated with geo-referenced environmental factors (exposure to pollutants, noise, accessibility to healthcare services), behavioral information (lifestyle, diet, physical activity, therapeutic adherence) and socioeconomic variables (educational level, income, territorial vulnerability).

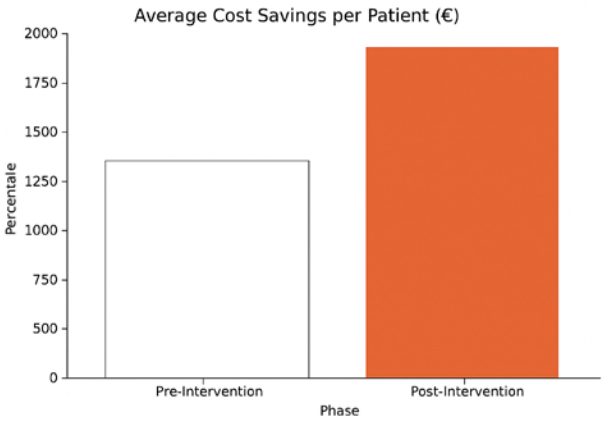
Before processing, the entire dataset was subjected to normalization, pseudonymization and ethical-legal compliance according to the GDPR and the guidelines of the Data Protection Authority, also following the principles outlined in the ethical framework of the Assisi Theorem regarding computational sustainability and algorithmic transparency.

This starting base has enabled the construction of a digital infrastructure suitable for experimenting with advanced predictive models, representing a realistic microcosm of the SSN and creating the conditions to evaluate – through in silico simulation – the clinical, economic and ethical impacts of introducing AI into personalized medicine. This approach enables a shift from reactive treatment to proactive monitoring, introducing a new care paradigm based on prediction, prevention and targeted intervention.









Indicator	Value
Patients involved in the simulation	10,000
Duration of the simulation	36 months
Estimated initial mean risk stimato	18%
Estimated mean risk after standard intenvention	12%
Estimated mean risk after intensive interven tion	6%
Projected ischemic events (baseline)	1,800 events
Estimated ischemic events post-intervention	950 events
Ischemic events prevented	850 events prvented
Average cost savings per patient	€1,900
Therapeutic adherence pre-model	61%
Therapeutic adherence post-model	84%

Appendix 2. Algorithmic Architecture of Clinical Prediction

Predictive algorithms used in precision medicine stand out not only for their mathematical architecture but also for their role in the clinical decision-making process, for the nature of the data they operate on, and for the degree of **interpretability** they offer—a crucial element in healthcare, where every decision must be justifiable, communicable, and traceable. The appropriateness of an algorithm is measured not only in terms of statistical accuracy but also in its **ability to adapt to clinical contexts**, generate trust among healthcare professionals, and comply with regulatory and normative requirements.

One of the most widespread and reliable algorithms is **Random Forest**, a supervised learning technique based on the construction of multiple decision trees trained on random subsets of the dataset and variables. This ensemble approach improves prediction stability and accuracy, reducing overfitting compared to individual trees. Random Forests are particularly suitable for classifying patients by disease risk, identifying strong predictive variables in noisy datasets, and providing an estimate of the relative importance of the features used. Although not easily interpretable at the individual case level, they offer a good balance between performance and transparency, making them suitable for clinical applications where also an **aggregated explanation** of the model's functioning is required.

An evolution of Random Forests is represented by **Gradient Boosting algorithms**, such as XGBoost or LightGBM, which build additive predictive models by iteratively improving the errors made by previous models. These algorithms achieve **very high accuracies**, especially in binary classification tasks (e.g., presence/absence of pathology) and regression, and are widely used in clinical predictive models. However, their interpretability is lower than that of linear models, requiring the use of local explainability techniques (e.g., SHAP – SHapley Additive exPlanations) to comply with the ethical and regulatory requirements of the medical environment.

When the analysis involves **sequential, longitudinal, or temporal data**, such as electronic health records updated over time, biometric signals, or series of clinical events, **Recurrent Neural Networks (RNNs)** and their evolutions, such as **Long Short-Term Memory (LSTM)** networks, become essential. These models are capable of learning long-term temporal dependencies and generating predictions in dynamic contexts, such as the risk of deterioration in chronic patients or response to treatment over time. Although powerful, RNNs often suffer from interpretability issues and require significant computational power, as well as careful handling of missing data and normalization.

More recently, **Transformer models**, originally developed in linguistics but quickly adapted to medicine (e.g., Med-BERT, GatorTron), have revolutionized the processing of textual and structured data in healthcare. Thanks to the **multi-head attention** mechanism, Transformers can analyze a patient's entire clinical context—exams, diagnoses, medications, reports—capturing complex relationships between events even if distant in time. Their flexibility makes them ideal candidates for clinical support systems integrated with electronic records. However, their black-box nature requires the use of advanced post-hoc explanation systems, and their clinical use is still subject to regulatory studies aimed at defining accountability standards.

Another highly valuable tool, especially in contexts where managing uncertainty is important, is represented by **Bayesian Networks**, which probabilistically model conditional dependencies between variables, generating explicitly interpretable predictions. These models offer **logical transparency**, as the entire inferential chain is visible and justifiable, and are particularly useful for integrating expert knowledge and observational data. They are ideal for simulating alternative clinical scenarios, evaluating trade-offs between risks and benefits, and structuring decisions in complex, high medico-legal responsibility contexts.

Generative models, such as **Generative Adversarial Networks (GANs)** or **Variational Autoencoders (VAEs)**, are playing an increasing role in clinical simulations, in the creation of virtual cohorts, and in augmenting datasets in situations where real-world data is scarce. Although not intended for direct explainability, their ability to generate realistic synthetic data, complete incomplete datasets, and test therapeutic hypotheses in simulated environments represents a revolutionary potential for in silico medicine and for virtual preclinical validation of drugs and devices.

Each algorithm has its own **distinct clinical vocation**, determined by the type of data processed, the decision-making context, the need for transparency, and the regulatory maturity. The choice of the ideal algorithm is not merely technical but **a strategic act that reflects the ethical, clinical, and economic priorities** of the healthcare system intending to adopt

it. Precision medicine, when well conducted, is not only the place where models are built but **the field where the right tools are consciously chosen to improve people lives.**

Random Forests and Gradient Boosting

Ensemble models based on decision trees, such as **Random Forests** and **Gradient Boosting** techniques, represent one of the most effective and widespread predictive architectures in computational medicine, especially for classifying patients into **risk groups** and identifying **determinant variables** in pathological or therapeutic processes. These models are based on the idea that combining multiple weak predictors—such as individual decision trees—can produce **a more robust, accurate, and generalizable global model**.

In the case of Random Forests, the mechanism relies on building numerous independent trees, each trained on a random subset of the dataset (bootstrap sampling) and with random variable selection at the root of each split. The aggregation of the final results typically occurs through majority voting in the case of classification or arithmetic mean for regression. This approach drastically reduces the risk of overfitting typical of single trees, improving prediction stability and ensuring a good generalization capability on previously unseen patients.

One of the most appreciated features of Random Forests in clinical settings is the ability to calculate so-called **feature importance**, a quantitative estimate of each variable's influence on the model's decision-making process. This is particularly useful for healthcare professionals and researchers, who can not only obtain a prediction but also understand **which clinical, genetic, or environmental factors have driven that prediction it**. For example, in a cardiovascular risk model, the system might highlight that glycemic variability, homocysteine levels, and family history are the three main drivers of a patient's classification as "high risk."

In parallel, **Gradient Boosting models** like **XGBoost, LightGBM,** and **CatBoost** represent an advanced variant of the ensemble principle. In this case, trees are built sequentially, and each new tree is trained to correct the residual errors of the previous model. This incremental mechanism leads to greater **predictive accuracy**, especially in complex problems, but requires greater care in parameter tuning to avoid overfitting and is more computationally demanding. Even in these models, feature importance analysis is supported and can be further explored through local explanation techniques like SHAP, which allow **to attribute specific weights to variables for each individual prediction** and make the output compatible with ethical requirements for transparency and clinical accountability.

The effectiveness of ensemble models has proven particularly high in contexts with **heterogeneous, high-dimensional datasets and missing data**—typical conditions in real-world clinical registries. For this reason, they are now employed in a wide range of predictive applications: from risk stratification in oncology or diabetes patients, to predicting drug responses, to early identification of cognitive deterioration in subjects at risk of dementia.

Decision tree-based ensemble models offer an **excellent balance between predictive power and interpretability**, making them ideal for use in clinical decision-making support systems, in regulated environments, and in advanced preventive screening programs. Their modular structure also allows easy integration into bioinformatic pipelines and clinical-digital workflows, positioning them as **privileged tools in high-responsibility predictive medicine**.

Recurrent Neural Networks (RNNs) and Transformers

Algorithms designed for processing **sequential and temporal data** have revolutionized computational medicine's ability to interpret dynamic and longitudinal phenomena, such as disease progression over time, response to successive treatments, or trends in vital parameters. In this area, **Recurrent Neural Networks (RNNs)**—and their more stable evolution, **Long Short-Term Memory (LSTM) Networks**—have represented the standard for sequence modeling for years, thanks to their intrinsic ability to **retain memory of previous information**. This feature allows them to capture **long-term temporal dependencies**, which are crucial for predicting future events starting from a complex clinical history.

A typical example of their use is the predictive analysis of longitudinal electronic health records: through LSTMs, a model can be trained to recognize temporal patterns in laboratory data, administered medications, reported symptoms, or previous outcomes, and from there, infer the probability of imminent hospitalization, therapeutic failure, or critical events like a heart attack or hypoglycemic crisis. Similarly, in the field of **physiological signals**, RNNs are used to analyze

electrocardiograms (ECGs), sleep tracings, or respiratory signals, providing early warning systems for clinical intervention.

However, RNNs and LSTMs have some **structural limitations**. Their sequential architecture involves step-by-step data processing, making training computationally expensive and difficult to scale on very large datasets. They also suffer from the vanishing gradient problem, which limits their effectiveness on very long sequences or in contexts with high semantic complexity.

To overcome these limitations, **Transformer models** have gained prominence in recent years, originally developed in the field of Natural Language Processing but rapidly adapted to the healthcare domain. The innovative core of Transformers lies in the **multi-head attention mechanism**, which allows the model to "look" simultaneously at all positions in the sequence and weigh the relative importance of each element against the others. This approach is particularly suited for modeling c**omplex, non-linear, and non-local relationships**, such as those between a genetic mutation and a late effect, or an initial therapy and a subsequent clinical complication.

In clinical settings, this revolution has led to the emergence of **biomedical foundation models** like **Med-BERT, ClinicalBERT, GatorTron, and BioGPT**, pre-trained on billions of words from clinical records, scientific publications, and healthcare databases, then fine-tuned for specific tasks such as mortality prediction, report analysis, or automatic diagnosis classification. These models not only achieve superior predictive performance but also possess semantic capabilities that allow **contextual understanding of clinical languag**e, maintaining coherence between medical events even across extended time horizons.

Despite their power, Transformers pose significant challenges in terms of interpretability, energy consumption, and engineering complexity. For this reason, their clinical use is contingent upon the development of post-hoc explainability techniques and rigorous validation in regulated environments. However, the potential they offer in building adaptive, multimodal, patient-centered predictive systems is extraordinary and represents one of the most promising directions for the future of precision medicine.

The evolution from LSTMs to Transformers marks **an epochal shift** in temporal data modeling in healthcare. It is not merely a matter of numerical performance but of a new ability to **understand and contextualize the patient's history**, integrating temporal, semantic, and biological dimensions into a predictive vision that increasingly approaches the level of human complexity.

Bayesian Networks

Bayesian networks represent one of the most powerful mathematical architectures for modeling the complexity of clinical and biological reasoning. They are **probabilistic graphical structures** where variables—clinical, omic, environmental, or behavioral—are represented as nodes, and the conditional dependence relationships between these variables are expressed by directed edges forming a acyclic graph. This representation not only makes **causal or associative interactions** explicit but also **enables transparent probabilistic inferences**, i.e., deductions on the probability of a specific clinical event occurring based on a set of partial observations.

In the context of precision medicine, Bayesian networks are particularly valuable because they formalize how partial and uncertain information combines, accounting for individual variability and the dynamic evolution of clinical pictures. For example, in a Bayesian model incorporating genomic data, proteomic profiles, environmental risk factors, and family history, it is possible to estimate—with mathematical transparency—the conditional probability that a patient will develop a neurodegenerative disease within the next five years. Every knowledge update (e.g., adding a newly detected genetic mutation or a clinical symptom) results in an automatic and coherent update of the probability distribution over other events, according to the rules of Bayesian theory.

This makes Bayesian networks **extremely suitable for decision medicine**, i.e., clinical contexts where the physician must make a decision based on multiple, uncertain or incomplete factors, and a **clear justification of choices** is required—not only for ethical and deontological reasons but also to comply with healthcare regulations and engage in dialogue with patients and families. Unlike deep learning models, which often offer opaque predictions, Bayesian networks allow **visualization of the entire inferential process**, making every step comprehensible and traceable—a crucial feature in clinical decision support systems regulated by bodies like EMA or FDA.

From a technical standpoint, Bayesian networks are divided into two main classes: **static Bayesian networks**, which model relationships between variables at a single time point, and **Dynamic Bayesian Networks**, which extend the model to the temporal domain, making them suitable for longitudinal scenarios like chronic disease monitoring or predicting clinical events over time. Moreover, many modern networks incorporate **hybrid structures**, where discrete variables (e.g., presence or absence of a symptom) and continuous variables (e.g., blood levels, age, blood pressure) coexist within the same graph, expanding the range of modelable situations.

No less important is their **ability to integrate expert knowledge and observational data**, i.e., building the model from both statistical evidence and well-established clinical rules. This allows, for example, to initiate model training even under conditions of data scarcity and to progressively adapt it as data becomes available, maintaining **a link between medical theory and machine learning**.

In summary, Bayesian networks represent **a bridge between explicit clinical knowledge and automatic statistical modeling**, a tool that combines mathematical rigor, semantic flexibility, and inferential transparency. Their application in precision medicine allows to consciously approach biological uncertainty, manage the complexity of healthcare big data, and **support medical decisions that are not only correct but also comprehensible, justifiable, and shareable**. For these reasons, Bayesian networks are today considered one of the theoretical pillars for building truly predictive, participatory, and personalized medicine.

Generative Adversarial Networks (GANs)

Generative Adversarial Networks (GANs), known as **antagonistic generative models**, represent one of the most significant innovations in artificial intelligence applied to precision medicine. These architectures are based on the interaction between **two distinct yet interdependent neural networks**: the **generator**, tasked with producing synthetic data similar to real-world data, and the **discriminator**, tasked with distinguishing real-world data from generated data. The system's goal is to reach a dynamic equilibrium where the generator becomes so effective that it manages to "fool" the discriminator, producing data so realistic that it is indistinguishable from real-world data.

This controlled competition structure allows GANs to learn the underlying statistical distributions of clinical, biological, or imaging data in an unsupervised manner and to **generate new plausible examples** that adhere the learned regularities. The potential of this technology in precision medicine is extraordinary and manifests in several highly sensitive and strategic areas.

One of the main uses of GANs is in simulating rare patients or pathological conditions underrepresented in clinical datasets. In many genetic, oncological, or autoimmune diseases, data scarcity makes it difficult to train reliable predictive models. GANs enable artificial dataset expansion by generating synthetic clinical profiles consistent with known pathophysiology, which can be used to test algorithms, train neural networks, or perform regulatory simulations. This approach is particularly useful in pediatric or geriatric contexts, where ethics limits data acquisition.

A second fundamental application area is the generation of synthetic medical images for training deep learning-based automated diagnosis systems. For example, GANs have been used to create realistic images of MRIs, CT scans, digital histologies, and mammograms that retain essential structural characteristics but contain no identifiable patient data, ensuring privacy and anonymity. These images can be employed to **balance imbalanced datasets**, reduce overfitting in models, and provide educational material in environments where access to real-world images is limited.

A further strategic use lies in the **prediction of incomplete or ethically unexplorable clinical scenarios**. Indeed, GANs can generate simulations of virtual patients subjected to hypothetical conditions—e.g., sudden treatment interruption or exposure to an environmental risk—without exposing any human to such conditions. This enables in silico exploration of extreme or low-probability scenarios, improving the predictive capacity and **proactive response of clinical systems**.

Despite their power, GANs also present challenges. From a computational standpoint, training is complex and unstable, requiring precise parameter selection and often a significant amount of initial data to produce valid results. Moreover, their highly flexible nature carries **risks of generating artifactual or clinically invalid data** if not accompanied by expert supervision and rigorous validation procedures. The lack of model interpretability remains a further limitation for their direct application to clinical decisions.

To address these issues, hybrid forms like **Conditional GANs (cGANs)** are being developed, where generation is guided by structured inputs (e.g., a diagnosis, age, sex), as well as **Wasserstein GANs (WGANs)**, which introduce more stable metrics for distribution distances. Additionally, new frontiers like **GANs integrated into digital twins** promise fully **personalized virtual clinical avatars** which can be used to realistically and dynamically test treatment efficacy, predict complications onset, and experiment with personalized therapies.

GANs are not merely tools for creating "fake" data but true **knowledge-generating machines**, capable of extending the scope of clinical experimentation beyond the limits imposed by empirical reality. If integrated responsibly, validated by scientific communities, and regulated by authorities, Generative Adversarial Networks can **become strategic allies in building a predictive, equitable, simulative, and deeply respectful medicine that honors human dignity**.

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