Review

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Status of the implementation of pharmacogenetics in clinical practice in Spain: from regional to national initiatives

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Abstract

Introduction: Pharmacogenetics (PGx) has the potential to improve patient care, allowing to transform medical interventions by providing personalized therapeutic strategies. Scientific evidence supports the use of PGx in clinical practice and international organizations are developing clinical guidelines to facilitate the utilization of PGx testing. However, clinical implementation of PGx is limited and unequal worldwide.
Content: This review summarizes regional and national Spanish initiatives to implement PGx in the clinical practice.

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Summary and Outlook: Diverse strategies to implement PGx in healthcare are applied across countries or even in the different regions of a specific country. Such was the case of Spain, a European country with 17 Autonomous Regions and two Autonomous Cities, each one with capacity to manage their own healthcare systems. Nevertheless, during the past years, many initiatives and strategies have been launched in Spain to develop different aspects of PGx. Importantly, the National Healthcare System has approved a PGx testing catalogue. This review highlights the crucial work and efforts of scientific societies (like the Spanish Society of Pharmacogenetics and Pharmacogenomics), of experts in PGx, of healthcare providers and of governmental parties in the implementation of PGx to personalize patient therapy, focused in Spain.

Keywords: clinical implementation; personalized medicine; pharmacogenetics; pharmacogenomics; Spanish national healthcare system

Introduction

Pharmacogenetics (PGx) has the potential to immediately impact the care of patients in a clinically meaningful manner. The scientific evidence supporting the use of PGx in clinical practice is high and there is an important demand for its clinical implementation [1]. Personalised Medicine (PM), based on comprehensive genomic and diagnostic characterization, has the potential to transform medical interventions by providing effective and tailored therapeutic strategies, and it has become a real need [2]. Unfortunately, during the past decades, the implementation of PGx in clinical practice has been limited due to the lack of consistency in clinical recommendations. To bridge the knowledge gap in PGx, several organizations have developed valuable information under the form of clinical guidelines, including the Clinical Pharmacogenetics Implementation Consortium (CPIC) [3], the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) [4], the Dutch Pharmacogenetics Working Group (DPWG) [5] and the French National Network of Pharmacogenetics (RNPGx) [6]. Nevertheless, implementation of PGx is unequal worldwide, with different strategies applied across the countries or even in the different regions of a specific country. Spain, with 17 Autonomous Regions and two Autonomous Cities, each one with capacity to manage their own healthcare systems, was an example of the latter. Although some regions started PGx initiatives years ago, it has been recently when many strategies have been launched to develop different aspects regarding PGx implementation in the clinical practice across the country. Importantly, a national strategy for PM, serving as a general framework for its implementation in the Spanish National Healthcare System (NHS) is crucial to guarantee technical quality, equal access of all citizens to the best practices and the sustainability of the healthcare system. Therefore, in 2018 the Spanish Senate delivered a proposal asking for a National Strategy on Genomics and Personalised Genomic Medicine [7]. As a consequence, in 2020 the national government planned to invest €25 million into Predictive Medicine, Data Science and Genomic Medicine over the following three years under a project called Infrastructure of Precision Medicine associated with Science and Technology (IMPaCT) [8]. The effort is resulting in the creation of a national cohort for research, as well as an integrated clinical and genomic data infrastructure at the national level.

Moreover, the primary professional scientific non-profit society for pharmacogenetics and pharmacogenomics in Spain, the Spanish Society of Pharmacogenetics and Pharmacogenomics (*Sociedad Española de Farmacogenética y Farmacogenómica*–SEFF, https://seff.es/), founded in 2005, is actively working on the translation of PGx information into today's healthcare, as well as supporting clinical implementation both on a national and clinical laboratory level. In the last few years, the SEFF has been working on the elaboration of clinical guidelines in order to offer PGx counselling for Spanish speaking healthcare professionals in Spain and also in Latin America. In this sense, the key role of clinical pharmacology, hospital pharmacy, biochemistry and genetics societies in leading PGx initiatives has been previously described [9]. Thus, SEFF is bringing together the efforts of experts from a variety of fields–clinical pharmacologists, geneticists, clinicians, and pharmacists–to provide the necessary guidance to bridge the gap between PGx research and the clinic.

It's also worth mentioning that early this year thanks to the efforts of several experts, representatives from the Autonomous Communities and Spanish scientific societies, a national common portfolio of services in the area of genetics has been presented by the NHS in order to guarantee a more homogeneous and equitable access. Indeed, this portfolio contains the first PGx catalogue approved at a national healthcare level in Europe.

This review sets the focus on regional and national Spanish initiatives to implement PGx in the clinical practice.

Methods

The information included in this review has been collected from different sources [1]: PubMed database [2]; Institutional resources and web pages [3]; Spanish hospitals' service portfolio – when available in hospital's website, PGx information has been obtained and included in the revision. Please note that this information is subjected to be the latest update of the Hospital's webpage [3]; Direct contact with

healthcare professionals at Spanish hospitals – when possible, direct contact with the Pharmacy or Clinical Pharmacology or Clinical Analysis units from hospitals has been established in order to collect first-hand updated information. All the information provided by the Hospitals' units have been included. Available information regarding PGx tests is indicated in Table 1 and represent information as of 2023, before the presentation of the national genetic catalogue in January 2024.

Spanish regional initiatives

In this section, an overview of the main Spanish regional PGx initiatives is given.

Andalusia

Andalusia had an unequal implementation of PGx across the region without any regional initiative in the Andalusian Health System. In western Andalusia, Hospital Universitario Virgen Macarena (HUVM) [10] and Hospital Universitario Virgen del Rocío (HUVR) in Seville had implemented PGx of some genes in the clinical practice (Table 1). Additionally, HUVM was involved in a multi-centric PGx pilot project, in collaboration with the Human Genotyping Unit at the Spanish National Cancer Research Centre (CEGEN-CNIO, Madrid), to evaluate the barriers in the implementation of PGx through the complete characterization of a subset of the Andalusian population [11].

On the contrary, in eastern Andalusia, there were two specific PGx units in public hospitals, one in San Cecilio Clinical University Hospital (HUCS) and another in Virgen de las Nieves University Hospital (HUVN) with different levels of implementation (Table 1). Of note, the Pharmacy Service of HUCS had been part of the H2020 project entitled "*Ubiquitous Pharmacogenomics (U-PGx): Making actionable pharmacogenomic data and effective treatment optimization accessible to every patient*" in which around 8,100 patients from 7 European countries were recruited and treatments adjusted based on PGx information [12].

Additionally, the Andalusian community developed an ambitious Program of Personalized Medicine [13]. This program started in 2010 with the Medical Genome Project whose aim was to address the sequencing of human genomes of phenotyped patients and control individuals [14]. This program allowed the creation of the Collaborative Spanish Variant Server (CSVS), a reference database of the genomic variation in the Spanish population [15]. Recently, PGx information have been included in CSVS to use as reference of the PGx alleles in

Table 1: Spanish centers of the public National Healthcare System with pharmacogenetic implementation prior to the NHS PGx approval.

Spanish region	City	Hospital/Centre	Department	Laboratory	<5 genes	5–10 genes	>10 genes	PGx report	External service	Source of data
Andalusia	Sevilla	Hospital Universitario Virgen del Rocío	Pharmacy/Pharmacology	Clinical Analysis	●					Provided by Hospital
Andalusia	Sevilla	Hospital Universitario Virgen Macarena	Pharmacy	Biochemistry	●					Provided by Hospital
Andalusia	Cádiz	Hospital Puerta del Mar	Pharmacy	Clinical Analysis	●					Hospital's service portfolio
Andalusia	Granada	Hospital Universitario Virgen de las Nieves	Pharmacy	Pharmacogenetic	●			●		Provided by Hospital
Andalusia	Granada	Hospital Universitario Clínico San Cecilio	Pharmacy	Genyo		●		●		Provided by Hospital
Andalusia	Malaga	Hospital Universitario Carlos Haya	Pharmacy		●				●	Provided by Hospital
Aragon	Zaragoza	Hospital Miguel Servet	Pharmacy	Genetics	●					Provided by Hospital
Asturias	Oviedo	Hospital Universitario Central de Asturias	Genetics and Molecular Oncology		●					Hospital's service portfolio
Basque country	Bilbao	Hospital Universitario Cruces	Clinical Analysis		●					Provided by Hospital
Basque country	Donostia-San Sebastián	Hospital Universitario Donostia	Clinical Analysis		●					Provided by Hospital

Table 1: (continued)

Spanish region	City	Hospital/Centre	Department	Laboratory	<5 genes	5–10 genes	>10 genes	PGx report	External service	Source of data
Castile-La Mancha	Toledo	Complejo Hospitalario Universitario de Toledo	Clinical Analysis		●					Provided by Hospital
Castile-La Mancha	Talavera de la Reina	Hospital Nuestra Señora del Prado	Clinical Analysis		●					Provided by Hospital
Castile-La Mancha	Ciudad Real	HU de Ciudad Real	Clinical Analysis		●					Provided by Hospital
Castile-La Mancha	Cuenca	Hospital Virgen de la Luz	Clinical Analysis		●					Provided by Hospital
Castile-La Mancha	Albacete	Complejo Hospitario Universitario de Albacete	Clinical Analysis		●					Provided by Hospital
Catalonia	Barcelona	Hospital de la Santa Creu i Sant Pau	Pharmacy/Genetics	Genetics			●	●	●	Provided by Hospital
Catalonia	Barcelona	Hospital de la Vall d'Hebron	Pharmacokinetics and Pharmacogenetics Unit (Pharmacy)	Clinical Analysis		●		●	●	Provided by Hospital
Catalonia	Barcelona	Hospital Parc de Salut Mar	Pharmacy/Oncology	Molecular Biology Laboratory	●			●	●	Provided by Hospital
Catalonia	Barcelona	Hospital Clínic de Barcelona	Toxicology & Pharmacogenetics lab	Toxicology and Pharmacogenetics lab	●			●	●	Provided by Hospital
Catalonia	Badalona	Hospital Germans Trias i Pujol	Pharmacogenetics Unit	Clinical Analysis	●			●		Provided by Hospital
Catalonia	L'Hospitalet de Llobregat	Hospital Universitari de Bellvitge	Laboratory/Pharmacy	Clinical Analysis		●		●		Provided by Hospital
Catalonia	L'Hospitalet de Llobregat	Institut Català d'Oncologia - Hospitalet	Laboratory/Pharmacy	Molecular Biology Laboratory	●			●		Provided by Hospital
Catalonia	Terrassa	Hospital Universitari Mútua de Terrassa	Pharmacy/Genetics	Genetics	●			●	●	Provided by Hospital
Cantabria	Santander	Hospital Universitario Marqués de Valdecilla	Pharmacology		●					Provided by Hospital
Extremadura	Several cities	Hospitals, Mental Health and Primary Care Centres	Various services /Units	CICAB			●	●		For the full list of centres involved in MedeA Project consult: https://www.proyectomedea.es/equipo/
Extremadura	Badajoz	University Hospital of Badajoz	Pharmacogenetic	CICAB			●	●		MedeA Project
Extremadura	Coria	Hospital of Coria	Internal Medicine	CICAB			●	●		MedeA Project
Extremadura	Don Benito	Hospital Don Benito-Villanueva	Oncology	CICAB			●	●		MedeA Project
Extremadura	Llerena	General Hospital of Llerena	Psychiatry	CICAB			●	●		MedeA Project

Table 1: (continued)

Spanish region	City	Hospital/Centre	Department	Laboratory	<5 genes	5–10 genes	>10 genes	PGx report	External service	Source of data
Extremadura	Mérida	Hospital of Mérida	Rheumatology	CICAB			●	●		MedeA Project
Extremadura	Plasencia	Hospital Virgen del Puerto de Plasencia	Nephrology	CICAB			●	●		MedeA Project
Galicia	Santiago de Compostela	Fundación Pública Galega de Medicina Xenómica	Pharmacogenetics	Pharmacogenetics			●	●	●	Provided by FPGMX
La Rioja	Logroño	Hospital Universitario San Pedro	Clinical Analysis			●		●		Provided by Hospital
Madrid	Madrid	Hospital Universitario La Princesa	Pharmacology	Pharmacogenetic			●	●	●	Provided by Hospital
Madrid	Madrid	Hospital Universitario Gregorio Marañon	Pharmacy	Pharmacogenetic			●	●	●	Provided by Hospital and Portfolio
Madrid	Madrid	Hospital Universitario La Paz	Pharmacogenetic				●	●	●	Provided by Hospital
Madrid	Madrid	Hospital Universitario Ramón y Cajal	Genetics		●					Provided by Hospital
Madrid	Madrid	Hospital Clinico San Carlos	Laboratory/Pharmacology		●					Provided by Hospital
Madrid	Madrid	Hospital Severo Ochoa	Biochemistry		●					Provided by Hospital
Madrid	Madrid	Spanish National Cancer Research Centre (CNIO)	Human Genotyping Unit	Human Genotyping Unit			●	●	●	Provided by CNIO
Murcia	Cartagena	Hospitalario Universitario de Cartagena	Molecular Diagnostic laboratory			●		●		Provided by Hospital
Murcia	Murcia	Hospital Morales Meseguer	Haematology		●			●		Provided by Hospital and Portfolio
Murcia	Murcia	Hospital Virgen Arrixaca	Clinical Analysis			●				Provided by Hospital
Navarra	Pamplona	Hospital Universitario de Navarra	Genetics		●			●		Provided by Hospital
Valencian region	Valencia	Consorcio Hospital General Universitario de Valencia	Clinical Analysis	Genetics and molecular biology		●		●	●	Provided by Hospital
Valencian region	Valencia	Hospital de Sagunto	Clinical Analysis	Clinical Analysis	●			●		Provided by Hospital
Valencian region	Valencia	Hospital la Fe	Clinical Analysis	Clinical Analysis	●			●		Hospital's service portfolio
Valencian region	Valencia	Hospital Arnau de Vilanova	Clinical Analysis	Clinical Analysis			●	●		Provided by Hospital

this population. The Program of Personalized Medicine aimed at using patients' genomic data in the clinical practice thorough the development of a bioinformatics structure to manage genomic data in a scalable, equitable and affordable manner, compatible with the General Data Protection Regulation (GDPR). Lastly, Andalusia has developed an ambitious training program in Precision Medicine (PanMEP) [16].

Basque Country

At the administrative level, there is great interest in the implementation of personalized medicine (PM). This is reflected in the creation of the Planning and Management Committee for Personalized Medicine in the Basque Country in 2021 [17], the Basque Health Research and Innovation Strategy 2022–2025 [18], the Science, Technology and Innovation Plan 2030 (PCTI 2030) of the Basque Government [19], and the Basque Oncology Plan 2018–2023 [20].

PGx testing for *DPYD* (5-fluorouracil, in cancer), *CYP2C9* (siponimod, in multiple sclerosis), *UGTA1* (irinothecan, in cancer), and *CYP2D6* (eliglustat, Gaucher disease) were performed at the University Hospital Cruces and/or the University Hospital Donostia (Table 1). These tests were included in the service portfolio of Osakidetza, the Basque Health Service, and all the hospitals in the network had access to them. All petitioner physicians in the network also had access to the information about the test and the meaning of the variants. In some cancer types, tumour molecular testing was also available for treatment personalization. These techniques were implemented at the proposal of the interested services if there was a level of evidence and cost-effectiveness.

Canary Islands

The Canary medical council created in 2022 a specific commission for the development of PM. The PGx testing was included in the service portfolio of the Hospital Universitario de Canarias and the Hospital Universitario Doctor Negrín. The Institute of Technology and Renewable Energies (ITER) manages the supercomputer Teide–High Performance Computing and has a Genomics division specialized in next generation sequencing (panels, exomes and genomes) [21, 22]. ITER collaborates with the Hospital Universitario Nuestra Señora de La Candelaria (HUNSC) in research projects related to the development of PM in the Canary Islands. The project PHARMA-CAN aimed at improving drug prescription by taking into account the PGx allelic variation found in the Canarian population, using whole exome sequencing [23]. In addition, other projects focused on evaluating PGx using NGS were in progress. Besides, the Canary health service also collaborates with the IMPaCT project [8].

Castile and Leon

Castile and Leon was one of the most advanced regions in the implementation of PM in Spain at a regional level. In the clinical practice, two different protocols had been implemented: one protocol applied to diagnostics (particularly for rare diseases) with a network operation and a Regional Reference Unit on the Advanced Diagnostic of Rare Diseases (DiERCyL) [24]. And the second protocol, the 5SPM model (5 steps in PM) for the application of PGx in polymedication, carried out at the Complejo Hospitalario de Salamanca, where the specific Reference Unit for Pharmacogenetics and Precision Medicine in Castile and Leon is located [24].

In this Unit, more than 2000 cases of patients with adverse effects or therapeutic failure had been already analyzed, not only regarding their genetic factors, but also other characteristics that allow the personalisation of the therapy. This Unit has published in international journals good practice recommendations for PM and collected economic data indicate the benefit of using PM in therapy [25, 26].

In addition, this region set up the Network of Precision Oncopathology and was preparing the Strategic Plan for Personalised Precision Medicine, with the aim of implementing PGx. Castile and Leon is also involved in the IMPaCT Project, coordinating the Pharmacogenetics work package of the Genomic Medicine axis [8]. Also, the University Hospital of Burgos and the Foundation for Health Research (FBIS) participate in IPHARMGx project, a collaborative study on the implementation of PGx (see further details in the Madrid section).

Regarding research, the Instituto de Investigación Biomédica de Salamanca (IBSAL) has recently started a multicentric project on PGx in mental and cardiovascular health, funded by the call "Medicina Personalizada de Precisión" from the Health Strategic Action (AES) by the Spanish public health research institute Carlos III.

Catalonia

Catalonia had an unequal implementation of PGx across the region. Most hospitals that perform PGx studies were located in Barcelona. Some of them offered their services to external users, both for clinical and investigational purposes. The inequality was probably due to the lack of governmental initiatives for the implementation of germline PGx in Catalonia. In this sense, each hospital performed its own analyses.

Whereas *DPYD* was genotyped in most Catalan hospitals, other interesting genes such as the ones encoding cytochromes, were determined only in a small number of hospitals. Conversely, the situation for the determination of somatic biomarkers is better established. In 2021, the 'precision oncology program' was implemented in Catalonia (Servei Català de la Salut) [27]. This program is an approach to the diagnosis and treatment of cancer focused on the identification of subgroups of patients with certain cancers carrying specific molecular characteristics that can be eligible to receive targeted treatments with greater effectiveness. Its main objective is to guarantee equitable access to molecular determinations and targeted treatments for all patients in the region. This program has a field of action that includes all molecular or genetic alterations that are prognostic markers or predictors of therapeutic response. The identification of these markers determines the targets that should be considered in the development of more precise drugs, and in the indication of selected treatments for certain patients. The program is divided into four different areas: haematological tumours, solid tumours, paediatric tumours, and hereditary cancer.

More recently, on the 22nd February 2023, the document entitled 'Proposals to advance in the precision personalised medicine model in Catalonia' was presented (Consorsi de Salut I Social de Catalunya) [28]. More than 30 healthcare professionals from institutions and centers belonging to the Catalan public health system participated in it. The aim of this work was to identify the challenges to implement a PM model in this region, and to describe the measures needed to succeed.

Extremadura

In Extremadura, the implementation of PGx was being accomplished with a centralized initiative called "MedeA–Clinical implementation of pharmacogenetics and personalized drug prescription based on e-health" [29]. MedeA is a PM strategy which integrates PGx and relevant clinical data, to develop a decision-supporting tool to be used for individualized drug prescription during regular clinical practice within the context of e-health [30].

This initiative also sought the involvement of private companies through the use of innovative public procurement as an instrument to promote research, development and innovation in companies and within the framework of the Open Innovation Model promoted by the Extremadura Health Care Service and the Spanish Ministry of Science and Innovation. MedeA was designed and developed at the Clinical Research Center of the Extremadura University Institute for Biomedical Research (INUBE), where the PGx and Personalized Medicine Unit was created and is coordinating the project. MedeA involves many services/units from all hospitals in the regional Health Care Service, as well as numerous mental health and primary care centres across Extremadura (Table 1; and for the full list of hospitals and centers participating, consult the following link: https://www.proyectomedea.es/equipo/).

MedeA program main aims are to develop: 1) a personalized prescription program incorporated into the electronic medical records (EMR), 2) an artificial intelligence algorithm for the translation of individual's genetic information into phenotypes to facilitate drug prescription, 3) the necessary analytical and laboratory methods, and 4) methodologies to evaluate the pharmacological effects during patients' daily lives.

At the end, the project will allow clinicians to consult automatically information regarding the PGx background of the patients within the EMR of the regional Healthcare System, allowing them to select the most appropriate drug treatment options. In addition, as the first project in this sense, it would also allow validating this approach under real clinical conditions.

Galicia

The Galician Public Foundation of Genomic Medicine (FPGMX) centralizes the genetic testing from all hospitals within the Galician Health Service (SERGAS), thus covering 3.5 million inhabitants. FPGMX is specialized in genetics of hereditary diseases, oncohematology, prenatal diagnosis, genetic counseling, PGx and research activities. PGx testing was incorporated into the Galician health care portfolio in 2004 [31], since then clinicians are allowed to request this service. A number of PGx biomarker analyses to predict drug response had been implemented (Table 1). Once a specific analysis was performed a detailed PGx report was uploaded into the EMR of the patient. Additionally, since 2021, the FPGMX was entrusted with the management of an Implementation Plan of Pharmacogenetics in Psychiatry by SERGAS, as part of the Galician Mental Health Plan post-COVID-19 [32]. This plan aimed to implement the use of PGx in psychiatry, in order to reduce hospital admissions and adverse effects of treatment, as well as increase the efficacy of the treatment [33–35]. The FPGMX not only conducts PGx analyses in relation to long-acting antipsychotics, but also extends the scope to include other drugs [34–36].

From a research point of view, the FPGMX is actively working on establishing long-lasting multidisciplinary collaborations with medical and pharmaceutical teams to promote and coordinate translational projects in PGx. These activities

are developed in collaboration with different entities, such as the Santiago de Compostela Health Research Institute (IDIS), the Genomic Medicine Group, the Universidad de Santiago de Compostela (USC) and the Biomedical Research Network on Rare Diseases (CIBER).

At present, the FPGMX leads projects in different areas being some of the most recent: PM for the administration of methadone based on PGx profiles, optimization of schizophrenia treatment using OMIC data and systems biology (SchizOMICS), and omnigenic view of genetic susceptibility to severe COVID19 [31].

FPGMX is a member center of the Genomic Analysis Network within the Genomic Medicine Axis of the IMPaCT Platform [8]. Also, it is important to highlight that the FPGMX obtained funding and takes part in the Precision Medicine Research Projects (ISCIII) such as "Evaluation of a Proposal for the Implementation of Pharmacogenetics in the National Health System for Mental and Cardiovascular Health (Bio-FRAM)" and participates at "Clinical and PGx interventions in childhood and juvenile population (INGENIA)".

La Rioja

In order to advance in the implementation of PM, in 2016, La Rioja healthcare service created a Committee on Genetic Counselling to unify the petition and approval of genetic tests requested by the clinicians. The Clinical Analysis Laboratory at Hospital Universitario San Pedro performed PGx testing for *DPYD* (for fluoropyrimidine drugs), *UGT1A1* (irinotecan), *CYP3A5* (tacrolimus), *CYP2C9* (siponimod) and *SLCO1B1* (statins) [37]. Physicians in the public network were able to request these tests and also tumor molecular testing for treatment tailoring in certain tumor types. Moreover, the Hospital announced the creation of a Precision and Personalized Medicine Unit [38]. This Autonomous Community uses the EMR for each patient which also includes the genetic information that can be securely accessed by the specialist.

Regarding Research and Innovation Projects, the region launched the "Smart Specialization Strategy (RIS3, 2014–2020), the "V Plan Riojano de I+D+I" (2017–2020) and the "I Strategic Plan of Innovation in Health" (2017–2022) [39, 40]. Within these plans, PM is recognized as one of the future areas and is established as a funding priority. However, the specific objectives and measures to implement it need to be further developed. La Rioja also has a Biomedical Research Center (CIBIR) with research lines focusing on rare diseases, oncology, infectious diseases and neurodegeneration using next generation technologies and Big Data [41]. The CIBIR also counts with several Genomics & Bioinformatics and Biomedical Research platforms.

Madrid

In the region of Madrid, there is a regional initiative for the implementation of PGx under development. The main PGx units in public hospitals in this region are located in University Hospital (U.H.) La Princesa, U.H. Gregorio Marañón and U.H. La Paz (Table 1) [42–44]. These units also offer their services to external users, both for clinical and investigational purposes. In addition, some of these PGx units have demonstrated the utility of the implementation of pre-emptive PGx through research studies. Noteworthy, U.H. La Paz presented their experience after 3 years of pre-emptive PGx testing [45] and U.H. La Princesa is developing a multidisciplinary initiative named "PriME-PGX" to implement PGx in their hospital [46], and also contributing to the expansion of PGx knowledge among professionals, the general population and throughout the field of clinical trials. Other hospitals in the region that offered PGx tests in their service portfolios include U.H. Ramón y Cajal, U.H. Clínico San Carlos, U.H. Severo Ochoa and U.H. Fuenlabrada. The detailed level of PGx implementation of each hospital is showed in Table 1. In all cases, PGx reports include both genetic determination result and treatment recommendations (indication and or dose adjustments) for relevant gene-drug pairs. Moreover, research projects on PGx are developed at different hospitals and research centers such as IPHARMGx [47]. This is a National collaborative study, coordinated by the Clinical Pharmacology Department at U.H. La Paz, to evaluate the efficacy and cost-effectiveness of the implementation of PGx biomarkers through an anticipated genotyping strategy in the NHS. It involves more than 60 researchers from 11 hospitals (also in Madrid: U.H. Gregorio Marañón, Health Research Institute Gregorio Marañón and the Nephrology department at U.H. La Paz). Some of the axes of this study include PGx in kidney transplant patients and in high cardiovascular risk patient, among others. Additionally, Human Genotyping-CEGEN Unit at the Spanish National Cancer Research Centre (CNIO) offers a comprehensive PGx analysis, which includes 17 genes and 59 drugs to public hospitals of this region or other Spanish regions, facilitating their access to PGx analysis [48]. In this sense, a multicentric PGx pilot project in collaboration with different hospitals from Madrid, Balearic Islands and Andalusia is ongoing to evaluate the barriers of PGx implementation across the country in more than 300 Spanish patients. In addition, a recent study accomplished by CEGEN-CNIO in collaboration with the Clinical Bioinformatics Unit from HUVR has performed a comprehensive analysis of the genetic variability of 21 pharmacogenes in more than 3,000 Spanish individuals, evaluated the clinical impact on 64 drugs as well as determined PGx CNVs [49, 50]. Genetic data is available through the CSVS portal (http://csvs.babelomics.org/) [15].

Navarra

Until recently, the use and implementation of PGx in Navarre was mainly focused on the determination of tumor alterations (e.g. *ALK* translocations, *BRAF* and *EGFR* mutations, *BCR-ABL* fusion) and *HLA-B* typing. These tests were performed by the Anatomical Pathology, the Medical Genetics and the Immunology Departments of the University Hospital of Navarra (HUN) from the public healthcare system–Osasunbidea. Testing of *CYP2C9* and *DPYD* have also been incorporated into the clinical practice (Table 1).

The Navarre regional government has promoted strategic projects on Personalized Medicine (RETO GEMA) [51] and since 2016, the HUN and Navarrabiomed have pursued the implementation of genome sequencing as a clinical tool to develop personalized medicine in the public healthcare system (Nagen program [52]). Specifically to this review, the Pharmacy Service of the HUN and the Genomics Medicine Unit of Navarrabiomed developed PharmaNAGEN project [53]. This study evaluated the use of NGS as a clinical tool to obtain PGx data to improve treatment decisions in more than 250 individuals. The initiative aimed to develop a pharmacogenetic alert system implemented into the electronic clinical decision support system of the public healthcare. The prescription assistance tool, based on the individual PGx profile, will offer recommendations to clinicians to individualize the therapies. This will include recommendations for 52 drugs affected by the genotype of 13 genes. PharmaNAGEN paved the way for the implementation of PGx data in the healthcare system, acquiring the knowledge, developing the tools and training of clinical experts so that patients can benefit from personalized drug prescription [54, 55]. In addition, clinicians and researchers from the Biomedical Center of Navarre (Navarrabiomed), Navarra Services and Technologies (NASERTIC) and HUN are also participating in IMPaCT projects [8].

Valencian Community

In the province of Valencia, the University General Hospital of Valencia, Sagunto Hospital, La Fe Hospital and Arnau de Vilanova Hospital performed PGx testing. Each hospital performed its own analyses, ranging from a few genes to more than 10 genes, and provide with PGx reports. Moreover, various projects are currently being carried out for the implementation of PGx in clinical practice. IMPaCT project includes PGx within the IMPaCT-GENÓMICA program and its objective is to lay the foundations for the implementation of PGx tests in the NHS [8]. La Fe Hospital/Health Research Institute (IIS) in Valencia participate in this project in collaboration with other national centers [8]. Aligned with IMPaCT, the BioFRAM project aims at individualizing the prescription of drugs used in mental and cardiovascular diseases based on PGx markers for the prevention of adverse reactions. In this region, Hospital La Fe, Hospital Clínico, Hospital Doctor Peset and primary care centers are involved in this collaborative study.

In addition, the Pediatric Oncology Unit of Hospital la Fe together with the PGx Unit of IIS La Fe is carrying out, as part of the neuroblastoma European project 'HR-NBL2/SIOPEN', an independent work on the PGx of high-risk neuroblastoma patients to establish associations with drug side effects [56]. The abovementioned PGx Platform at IIS La Fe also investigates the association of PGx with immunosuppressants in organ transplantation, as well as it offers services to design PGx panels and validate PGx markers [57].

The PGx Platform of the Alicante Health and Biomedical Institute (ISABIAL) is currently participating in the project called IPHARMGx [47]. ISABIAL is also conducting a clinical trial (EudraCT Number: 2021-001238-21) entitled "Gender biases in pain medicine: from omics to healthcare" that integrates PGx, epigenetic, and metabolomic markers to understand the gender differences observed in the analgesic response to opioids.

Also, at Miguel Hernández University, a research project is being developed focused on the genetic variation and functional analysis of cytidine deaminase enzyme (CDA) activity to categorize it as a biomarker of oncological treatment toxicity [58].

Other Spanish regions

Some Spanish regions did not present a PGx clinical implementation structure although the main hospitals of these regions performed PGx testing for some genes (e.g. *DPYD*, *TPMT* or *UGT1A1)*.

This was the case of Aragon, although they showed interest in PGx and PM since 2010 [59], the implementation of PGx began at the end of 2020 with the *DPYD* alert from the Spanish Agency of Medicines and Medical Devices (AEMPS). Since then, genotyping of the population of the entire region was centralized at the Miguel Servet Hospital, located in Zaragoza, specifically at the Genetics Unit. The Pharmacy Department prepares the reports for each genotyped patient (Table 1).

In Asturias, the Genetics and the Molecular Oncology Units at the Central University Hospital of Asturias (HUCA) screen for *CYP2C9*, *CYP3A4* and *UGT1A* as per the hospital portfolio [60]. Also, the University of Oviedo and the Healthcare Research Institute of Asturias are participating in the IMPaCT project [8].

In Balearic Islands, the Son Espases Hospital set up the Genetic and Genomic Unit, which aims at acting as the diagnostic reference for genomic analysis in the regional healthcare service. Furthermore, the Clinical Analysis Unit of the Hospital includeed PGx testing in the portfolio, although it was not yet included in other hospitals. The region also collaborates with the IMPaCT project through the Health Research Institute of the Balearic Islands (IdISBa) [8].

In Castile-La Mancha, the main hospitals of Toledo, Ciudad Real, Cuenca and Albacete had implemented the PGx testing through their Clinical Analysis Units. They mainly performed the analysis of *DPYD* but also *CYP2C9* and *HLA-B* in some cases (Table 1). Also, researchers and clinicians from the Tomelloso Hospital and the Health Research Institute of Castile-La Mancha participate in the iPHARMGx project (already mentioned in the Alicante region) [47].

In Cantabria region, at the Marqués de Valdecilla University Hospital, *TPMT* polymorphism determinations were carried out in patients treated with azathioprine and *MTHFR* polymorphism determinations for hematological diseases. Negotiations were underway between the Molecular Genetics Service and Clinical Pharmacology of the same hospital to carry out laboratory tests by the Molecular Genetics Service, while the Clinical Pharmacology Service would prepare clinical reports for patients. Also, researchers and clinicians from the Marqués de Valdecilla University Hospital and Valdecilla Research Institute (IDIVAL) participate in the iPHARMGx project [47].

In Murcia, the Molecular Diagnostic Laboratory of the University Hospital Complex of Cartagena analyses *DPYD, UGT1A1, IL28, CYP2C9, CYP2C19* genes and the Genomics Laboratory of the Hematology Service of the University General Hospital Morales Meseguer studies *UGT1A1* and *DPYD* (Table 1) [61]. Both hospitals screen for somatic alterations with predictive value in neoplasias (e.g., *BCR-ABL, BRAF, EGFR, TP53)*. Hospitals from this region also collaborate with the IMPaCT project [8].

Spanish national initiatives

In this section, we provide information on the most important national PGx initiatives.

IMPaCT project

IMPaCT is the Precision Medicine Infrastructure associated with Science and Technology [8]. This infrastructure is designed to provide service to the research, development and innovation system oriented to PM, to promote the generation and transfer of high-quality knowledge in the NHS, ensuring scientific-technical excellence, equity and efficiency in the use of the available resources. The IMPaCT Strategic Plan is configured around three strategic axes (Predictive Medicine, Data science and Genomic Medicine) and two transversal strategic lines. The strategic axes are arranged in specific actions and work packages, with compliance indicators that should allow verifying the effectiveness of infrastructure deployment (Figure 1).

In a complementary way, the two transversal strategic lines are common to the above mentioned three axes and they provide internal coherence. The first transversal line refers to Ethics and scientific integrity, and the second one to Internationalization. This later aiming to position Spain as an international benchmark in the field of PM.

Specifically to the topic of this review, in the Genomic Medicine axis, one of the areas of application was PGx [62]. The main objectives of this part were to lay the foundation to allow PGx testing implementation in the NHS, and also to provide with genomic diagnostic services equitably across the country to individuals with serious drug or vaccine adverse events. This working group put all their efforts to: 1) connect with the Pharmacovigilance network and establish the samples workflow, 2) create Expert and Result Interpretation Committees, 3) establish and renew standardized laboratory protocols for drug adverse events, 4) elaborate Clinical Guidelines and a clinical report template, 5) provide diagnostic genomic services in a fair manner across Spain, 6) federated data sharing and data discovery, and 7) interrelate with the Predictive Medicine axis.

SEFF implementation strategy

There are many successful cases in which PGx was implemented in the clinical practice, where, based on the clinical guidelines established by the Clinical Pharmacogenetics Implementation Consortium (CPIC), genotyping began to be carried out prior to the prescription of certain drugs such as warfarin, clopidogrel, codeine, antidepressants and antiepileptics [3, 63–67].

Similarly to other national/international PGx groups, the Spanish Society of Pharmacogenetics and Pharmacogenomics (SEFF) is a national multidisciplinary scientific society actively working on the development of PGx guidelines in Spanish. The SEFF developed the *General Strategy for the Clinical Implementation of Pharmacogenetics* with the overall objective of generating recommendations for the implementation of the PGx to optimise the safety and efficacy of the pharmacological treatments taken by patients [68]. More than 50 experts in the field are working together organized in working groups (WG1. PGx regulation–List of

recommended drugs; WG2. Methodology and analytical interpretation; WG3. Clinical recommendations; WG4. Solid tumors) and programmes (1. Proficiency testing, 2. Teaching-training, and 3. Map of the labs and PGx services in Spain).

The advancement in PGx must be in line with therapeutic guidelines and regulatory agencies; however, progress in this area is often slow. As a consequence of this situation, the SEFF is working on the development of clinical recommendations based on the existing evidence, so that these can serve as a basis on which to start implementing PGx in the clinic [69]. So far, it has generated clinical recommendation documents for 12 gene – drug pairs that are available at the SEFF website (https://seff.es/), as well as published a consensus paper in collaboration with the Spanish Society of Medical Oncology for the genotyping of *DPYD* in cancer patients who are candidates for treatment with fluoropyrimidines [70]. More documents are in progress. With this strategy, SEFF wants to become a fundamental element in the Spanish Strategy for Personalised Medicine promoted by the National Government and to facilitate the implementation of the current NHS PGx portfolio.

National PGx implementation strategy

At the national level, a Working Group of experts reporting to the Healthcare Ministry has been working on updating and specifying a common portfolio of services in the area of genetics for the NHS in order to guarantee a more homogeneous and equitable access to all individuals who require these tests within the NHS.

The first version of the catalogue, that will need continuous updating, was approved in the plenary session of the Interterritorial Council of the NHS on June 23rd 2023, and presented it on January 23rd 2024 by the Healthcare Ministry [71]. The proposed catalogue was developed by eight subgroups, with the participation of representatives from the Autonomous Communities, Spanish scientific societies, the health research institute Carlos III (ISCIII) and the Network of Agencies for Assessing NHS Technologies and Performance, for these prioritized areas: adult onco-hematology, pediatric onco-hematology, pharmacogenomics, heart disease and disorders of the circulatory system, ophthalmological diseases, hereditary metabolic and mitochondrial diseases, neurological diseases and neuromuscular/neurodevelopmental disorders including cognitive deficits.

It is worth mentioning that this is the first PGx catalogue approved at a national healthcare level in Europe. It includes 12 genes, for 22 main drugs and the clinical indication criteria for each test (Table 2 and in the link: https://cgen.sanidad.gob.es/#/consulta-general). Information on the type of technique and the indispensable variants is also included, and it is warned that the obtained genetic information can be used for the adjustment of other treatments that also have specific recommendations. In addition, the Spanish Agency for Medicines and Medical Devices (AEMPS, abbreviation in Spanish) has recently published a database with PGx biomarkers to facilitate the implementation of PGx in the clinics (https://www.aemps.gob.es/medicamentos-de-uso-humano/base-de-datos-de-biomarcadores-farmacogenomicos/). This resource

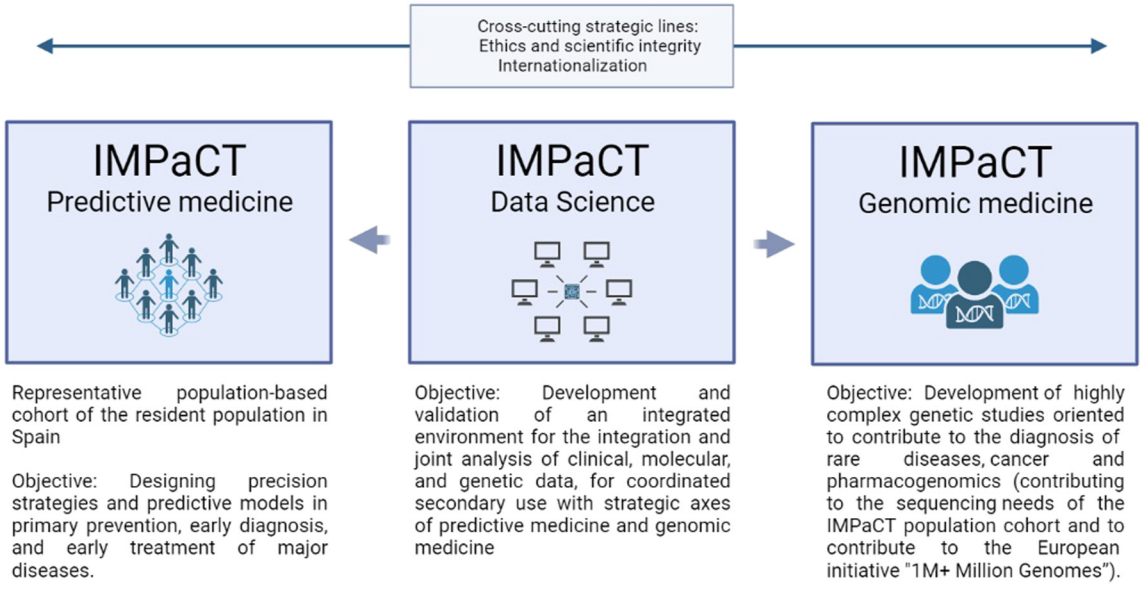

Figure 1: Strategic axis of IMPACT project.

provides with the regulatory information included in drug data sheets, and in the near future, it will also contain the established recommendations for each active compound.

Once the appropriate regulatory development is in place, each Autonomous Community will need to establish the necessary circuits to ensure adequate patient access. To this end, some regional groups have already started working, and important developments will come throughout this year.

Overview of PGx practice in other countries

Although this review focuses in Spain, PGx implementation approaches have been launched and developed worldwide since the early 2000s. Therefore, we deemed necessary to give a broader overview of these initiatives (summary tables with main worldwide PGx initiatives are available in [72, 73]).

In the United States, several institutions are involved in projects such as the Electronic Medical Records and Genomics Network–Pharmacogenomics Study (eMERGE-PGx) [74], Implementing GeNomics In practice (IGNITE) [75], the St. Jude Children's Research Hospital institution-wide pre-emptive pharmacogenomics program (PG4KDS) [76], the Pharmacogenomics Research Network (PGRN) [77] or the Pharmacogenomics Resource for Enhanced Decisions in Care and Treatment (PREDICT) [78], among others. In Europe and Canada pre-emptive single gene testing have been implemented as examples of clinically actionable PGx testing with sufficient clinical evidence for patient benefit. One example being *DPYD* genotyping in patients prior to

Table 2: Recommended pharmacogenetic tests in the Spanish Public National Healthcare System.

Drug	Gene	Essential alleles
Abacavir	*HLA-B*	*HLA-B**57:01
Allopurinol	*HLA-B*	*HLA-B**58:01
Atazanavir	*CYP2C19*	*2, *3, *4, *17
Azathioprine	*NUDT15*	*2, *3
Azathioprine	*TPMT*	*2, *3A, *3B, *3C, *4
Capecitabine	*DPYD*	NM_000110.3(*DPYD*): c.1905+1G>A (*2A), c.1679T>G (*13), c.2846A>T, [c.1129–5923C>G/c.1236G>A](HapB3)
Carbamazepine	*HLA-A*	*HLA-A**31.01
Carbamazepine	*HLA-B*	*HLA-B**15:02
Clopidogrel	*CYP2C19*	*2, *3, *4, *17
Eliglustat	*CYP2D6*	*3, *4, *5, *6, *9, *10, *17, *29, *36, *41, copy number variants
Fluorouracil	*DPYD*	NM_000110.3(*DPYD*): c.1905+1G>A (*2A), c.1679T>G (*13), c.2846A>T, [c.1129–5923C>G/c.1236G>A](HapB3)
Irinotecan	*UGT1A1*	*28
Ivacaftor	*CFTR*	NP_000483.3(CFTR): p.F508del (c.1521_1523delCTT), p.R117H (c.350G>A), p.G178R (c.532G>A), p.S549R (c.1645A>C), p.S549 N (c.1646G>A), p.G551S (c.1651G>A), p.G551D (c.1652G>A), p.G1244E (c.3731G>A), p.G1349D (c.4046G>A), p.S1251 N (c.3752G>A), p.S1255P (c.3763T>C)
Mercaptopurine	*NUDT15*	*2, *3
Mercaptopurine	*TPMT*	*2, *3A, *3B, *3C, *4
Omeprazole	*CYP2C19*	*2, *3, *4, *17
Oxcarbazepine	*HLA-B*	*HLA-B*15:02*
Phenytoin	*HLA-B*	*HLA-B*15:02*
Pimozide	*CYP2D6*	*3, *4, *5, *6, *9, *10, *17, *29, *36, *41, copy number variants
Rasburicase	*G6PD*[a]	NM_001360016.2(*G6PD*): c.563C>T, c.844G>C, c.376A>G/c.680G>T, c.376A>G/c.202G>A, c.376A>G/c.968T>C, c.376A>G/c.95A>G, c.1360C>T, c.1376G>T
Simvastatin	*SLCO1B1*	NM_006446.5(*SLCO1B1*): c.521T>C (*5 or *15)
Siponimod	*CYP2C9*	*2, *3
Tegafur	*DPYD*	NM_000110.3(*DPYD*): c.1905+1G>A (*2A), c.1679T>G (*13), c.2846A>T, [c.1129–5923C>G/c.1236G>A](HapB3)
Tetrabenazine	*CYP2D6*	*3, *4, *5, *6, *9, *10, *17, *29, *36, *41, copy number variants
Voriconazole	*CYP2C19*	*2, *3, *4, *17

[a]The frequencies of reduced function alleles in G6PD vary depending on the country and ethnic group. Therefore, G6PD genotyping must be studied individually. Some of G6PD alleles are included in this Table. Further information on the pharmacogenetic tests included in the catalogue of the Spanish National Healthcare System can be consulted in the link: https://cgen.sanidad.gob.es/#/consulta-general.

fluoropyrimidine chemotherapy [79–81]. Moreover, in the European Union, the Ubiquitous Pharmacogenomics Consortium has recently published the results of the PREPARE study [73, 82]. An open-label, multicentre, controlled, cluster-randomised, crossover implementation study of a 12-gene pharmacogenetic panel in seven European countries (Austria, Greece, Italy, the Netherlands, Slovenia, Spain, and the UK) demonstrating that genotype-guided treatment significantly reduced the incidence of clinically relevant adverse drug reactions and was feasible across diverse European health-care system organisations and settings [82].

Moving to Asia, the South East Asian Pharmacogenomics Research Network (SEAPharm) program was established by Korea, Indonesia, Malaysia, Taiwan, and Thailand, to conduct trial studies of adverse drug effects and develop guidelines adapted to Asian populations, which could guide drug use and prove useful in disease prediction/diagnosis [83, 84]. Other countries include Qatar, with the Qatar Pharmacogenetics Clinical Applications and Research Enhancement Strategies aiming to set a roadmap for optimizing PGx research and clinical implementation on a national scale [85]; Lebanon, with a handful of places performing PGx testing and/or research (e.g. the American University of Beirut Medical Center Molecular Diagnostics Laboratory) and participating in online Pharmacogenomics and Personalized Medicine (OPPM) courses in collaboration European partners and Egyptian institutions [86]; Australia, that recently conducted a national consultation commissioned by the Australian Genomics Health Alliance to identify and develop recommendations for research priorities for implementation of PGx testing in in the country [87, 88] or United Kingdom, where the UK Pharmacogenetics and Stratified Medicine Network, NHS England and Genomics England invited experts from academia, the healthcare sector, industry and patient representatives to come together to discuss the opportunities and challenges on the potential for implementing PGx into the NHS [89].

The abovementioned initiatives present a snapshot of the different stages of PGx implementation worldwide.

Challenges of PGx implementation

Although the clinical implementation of PGx has made significant progress and most agree on the relevance of PGx, a number of hurdles still need to be overcome. It is therefore crucial to outline the current problems to be solved and the challenges ahead. Some of these issues are related to the lack of pharmacogenetic knowledge and experience to interpret PGx results among the healthcare professionals [90, 91]. An extensive survey performed by Dutch pharmacists showed that, despite the general approval of the concept of PGx (99.7 %), less than 20 % of them had used PGx testing or felt adequately informed about PGx testing. Nevertheless, most presented a global interest (88.8 %) in receiving additional training on PGx [92]. Therefore, this aspect is considered a key barrier to translate PGx from research to clinical setting [93]. This could be circumvented with specific PGx education for clinicians, as shown in the U-PGx project where a variety of communication channels were needed throughout the PGx implementation [94]. Another example, in Spain, the SEFF teaching-training programme has developed a series of webinars in Spanish focused on PGx training for clinicians including information for the main genes and drugs used in the clinical setting [68].

Other important barrier to overcome is the lack of clear consensus guidelines in product labels and recommendations from different pharmacogenomic expert groups. Consensus of actionable pharmacogenomic labeling between the FDA and the EMA/FM has been identified only in 54 % out of 180 drugs with PGx information in both entities [95]. Therefore, this issue affects how PGx results are reported, as different guidelines may be applied by different hospitals in the same country. In addition, there is the absence of a standardized reporting format for PGx testing results [77], which seems to be mandatory to facilitate clinicians the understanding of PGx reports. In addition, other problem reported in the clinical setting is an unclear allocation of responsibilities among healthcare practitioners about who should discuss PGx with the patients and apply PGx results in their healthcare [96]. Therefore, a well-defined workflow is needed in any healthcare system to clearly stablish the way in which the PGx testing is ordered, interpreted, incorporated into the patient's clinical records, explained to them and applied in the routine practice.

On the other hand, on May 26, 2022, after a transitional period of 5 years, the new Regulation (EU) 2017/746 on *in vitro* diagnostic medical devices (IVDR) will fully replace Directive 98/79/EC on *in vitro* diagnostic medical devices (IVDD), aiming to enhance the safety, performance, and market regulation of IVDs, including genetic tests [97]. Therefore, PGx testing laboratories must prepare for significant changes, including stricter requirements for in-house devices (IH-IVDs), presenting challenges for innovation and the use of lab-developed tests. This new regulation could delay the implementation of the PGx setting in those laboratories not adapted enough.

Lastly, regarding the economic side, a complete review about the cost-effectiveness of PGx testing showed that 57 % drew conclusions in favour of PGx testing, of which 30 % were cost-effective (more effective at an acceptable additional cost) and 27 % were cost-saving (more effective at a lower cost). In addition, if genetic information was freely

available, 75 % of economic evaluations would support PGx-guided treatment, of which 25 % would be cost-effective and 50 % would be cost-saving [98]. In this line, pre-emptive genotyping strategy using a pharmacogenetic panel has shown effectiveness and feasibility across diverse European health-care system organisations and settings [82].

These are some of the main hurdles obstructing the implementation of PGx, some of which are currently being addressed by the ongoing initiatives. Moreover, legal and regulatory frameworks as well as ethical considerations (e.g., data protection, confidentiality, health inequalities and genetic diversity) need to be taken into account and further discussed among all parties involved (i.e., healthcare managers, providers, patient representative bodies, the general public, regulatory agencies and governments).

Conclusions

PGx is one of the core elements of PM, which is transforming clinical and biomedical research. Implementation of PGx is likely to be a major driver to mainstream genomics into clinical practice. Nevertheless, the use of PGx testing in routine healthcare is extremely slow and unequal worldwide due to several barriers such as the knowledge gap in PGx in healthcare providers, the modification of the current clinical workflows and infrastructure, as well as the cost effectiveness. In Spain, although the first autonomic communities developing PGx implementation date since 2004, it was not until recently that we experienced an increase in the development of PGx and PM implementation programs and studies. The application of PGx in clinical routine had remained limited due to the fact that Spain has 17 different Autonomous Communities, each one with capacity to manage their own healthcare system. However, thanks to the work and efforts of scientific societies such as the SEFF, of experts in PGx, of healthcare providers and of regional and national governmental parties, the adoption and implementation of PGx in Spain to personalize patient therapy is now a reality with the approval of a national PGx catalogue by the NHS.

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