Pharmacological Research 200 (2024) 107061

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Developments in pharmacogenetics, pharmacogenomics, and personalized medicine

Francisco Abad-Santos [a,*], Salvador F. Aliño [b], Alberto M. Borobia [c], Elena García-Martín [d], Patricia Gassó [e], Olalla Maroñas [f], José A.G. Agúndez [g,**]

[a] Clinical Pharmacology Department, Hospital Universitario de La Princesa, Universidad Autónoma de Madrid (UAM), CIBEREHD, Instituto de Investigación Sanitaria La Princesa (IP), Madrid, Spain
[b] Gene Therapy and Pharmacogenomics Group, Department of Pharmacology, Faculty of Medicine, Universitat de València, Av. Blasco Ibáñez 15, 46010 Valencia, Spain
[c] Clinical Pharmacology Department, La Paz University Hospital, School of Medicine, Universidad Autónoma de Madrid (UAM), IdiPAZ, Madrid, Spain
[d] Department of Pharmacology, Universidad de Extremadura, Avda de la Universidad s/n, 10071 Cáceres, Spain
[e] Basic Clinical Practice Department, Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona Clínic Schizophrenia Unit (BCSU), IDIBAPS, CIBERSAM, Barcelona, Spain
[f] Public Foundation of Genomic Medicine, Santiago University Hospital, Genomic Medicine group, Pharmacogenetics and Drug Discovery (GenDeM), CIBERER, Santiago Health Research Institute (IDIS), Galicia, Spain
[g] Universidad de Extremadura. University Institute of Molecular Pathology Biomarkers, Avda de las Ciencias s/n, 10071 Cáceres, Spain

ARTICLE INFO

Keywords:
Pharmacogenetics
Pharmacogenomics
Adverse drug reactions
Polymorphic drug metabolism
Clinical practice

ABSTRACT

The development of Pharmacogenetics and Pharmacogenomics in Western Europe is highly relevant in the worldwide scenario. Despite the usually low institutional support, many research groups, composed of basic and clinical researchers, have been actively working for decades in this field. Their contributions made an international impact and paved the way for further studies and pharmacogenomics implementation in clinical practice. In this manuscript, that makes part of the Special Issue entitled Spanish Pharmacology, we present an analysis of the state of the art of Pharmacogenetics and Pharmacogenomics research in Europe, we compare it with the developments in Spain, and we summarize the most salient contributions since 1988 to the present, as well as recent developments in the clinical application of pharmacogenomics knowledge. Finally, we present some considerations on how we could improve translation to clinical practice in this specific scenario.

1. Introduction

Western Europe is a key player in the fields of Pharmacogenetics, Pharmacogenomics, and Personalized Medicine. According to the Scopus database, as of July 24, 2023, Western European countries published about 18,500 research items on this field, as compared, for instance, with about 15,500 items published in the United States. The strong implication of Western Europe in this discipline is not surprising, given the crucial role that eminent Western European researchers played in its development (see, for instance, [1–8]). The focus on this discipline is, however, uneven among Western European countries. Fig. 1 shows a rough estimate of the focus in this discipline, by using a classification based on the Scopus database (accessed July 24, 2023), comparing the number of published items on pharmacogenetics or pharmacogenomics versus the total items published on all topics, in these countries. Greece, the Netherlands, and Spain are the top countries in such classification, above countries where this discipline was initially developed in Europe, such as Switzerland, Sweden, or Germany. When considering absolute values, Spain ranked also very high, only after countries with much higher research budgets according to Eurostat data, such as the United Kingdom, Germany, and Italy (Fig. 1). Of particular relevance is the case of France, which has about three times the research budget as compared to Spain, according to the gross domestic product and the percentage of it invested in research (https://www.imf.org/en/Home; https://www.eustat.eus/indice.html), is the third country in Western Europe in the number of total research items published, but it is under-represented in the percentage of these items focusing in Pharmacogenetics or Pharmacogenomics, as shown in Fig. 1. Fig. 2 summarizes the interactions

* Correspondence to: Clinical Pharmacology Department, Hospital Universitario de La Princesa, Universidad Autónoma de Madrid (UAM), CIBEREHD, Instituto de Investigación Sanitaria La Princesa (IP), Diego de León 62, 28006 Madrid, Spain.
** Corresponding author.
E-mail addresses: francisco.abad@uam.es (F. Abad-Santos), jagundez@unex.es (J.A.G. Agúndez).

https://doi.org/10.1016/j.phrs.2024.107061
Received 31 October 2023; Received in revised form 13 December 2023; Accepted 4 January 2024
Available online 8 January 2024

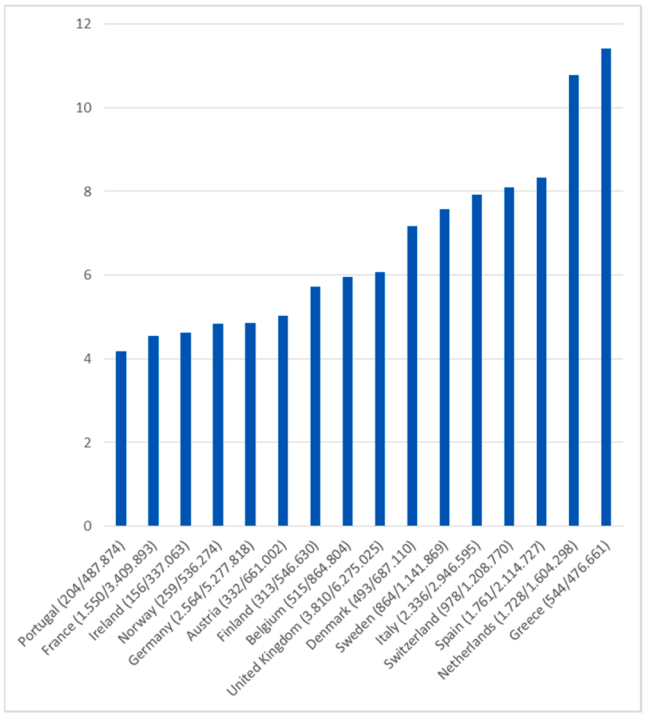

Fig. 1. Representation of the number of publications on pharmacogenetics or pharmacogenomics versus the total publications on all topics in Western European countries. Data correspond to a Scopus Search of the words pharmacogenetics OR pharmacogenomics in the title, abstract, or keywords, and the affiliation country, with no time limitation (accessed July 24, 2023). The Y axis was calculated by dividing the number of papers related to pharmacogenetics or pharmacogenomics, by the total number of papers published by every country, and the result was multiplied by 10.000. Raw data are included after the country label on the X-axis.

(co-authorship) between European countries in pharmacogenetics and pharmacogenomics research, based on the Scopus bibliographical search described above. After the prominent role of the United Kingdom, leading the number of publications and the network of interactions within Western European Countries, four countries show also a high degree of interaction. These are Italy, Germany, Spain, and the Netherlands. This manuscript is framed in the special issue Spanish Pharmacology and, therefore, we will describe the most salient achievements in this field in the specific scenario corresponding to this Special Issue.

In 1988, Prof. Julio Benítez published the first Spanish study on this topic, entitled "Debrisoquin oxidation phenotype in a Spanish population" [9]. The study was carried out in Badajoz. Prof. Benítez was introduced to this promising research field at the Prof. Sjöqvist group, at the Karolinska Institute where he investigated intoxications with tricyclic antidepressants [10,11]. Since then, several independent Spanish research groups actively investigated pharmacogenetics and pharmacogenomics, gradually increasing the scientific production until 2012. In 1993, the group led by Prof. Benítez published the first molecular pharmacogenetics paper where major differences in the frequency of *CYP2D6* SNPs, between Spanish and other European populations were described [12] with Spanish individuals showing a high frequency of rapid CYP2D6 metabolizers. These genetic differences between Spanish and other European individuals were further confirmed [13] and found to be even higher when a high frequency of carriers of *CYP2D6* multiple gene copies was reported in Spain, as compared to other European populations [14].

In 2012, a survey among members of the Spanish Societies of Pharmacology and Clinical Pharmacology was carried out to gather information on the barriers to implementing the use of pharmacogenomics testing [15]. This survey identified as major barriers in Spain the lack of institutional support for pharmacogenomics testing, and the lack of clinical practice guidelines. Also, this survey revealed that the gene-drug pairs identified as high-priority in Spain were roughly the same as those described in the USA in a previous study carried out among members of

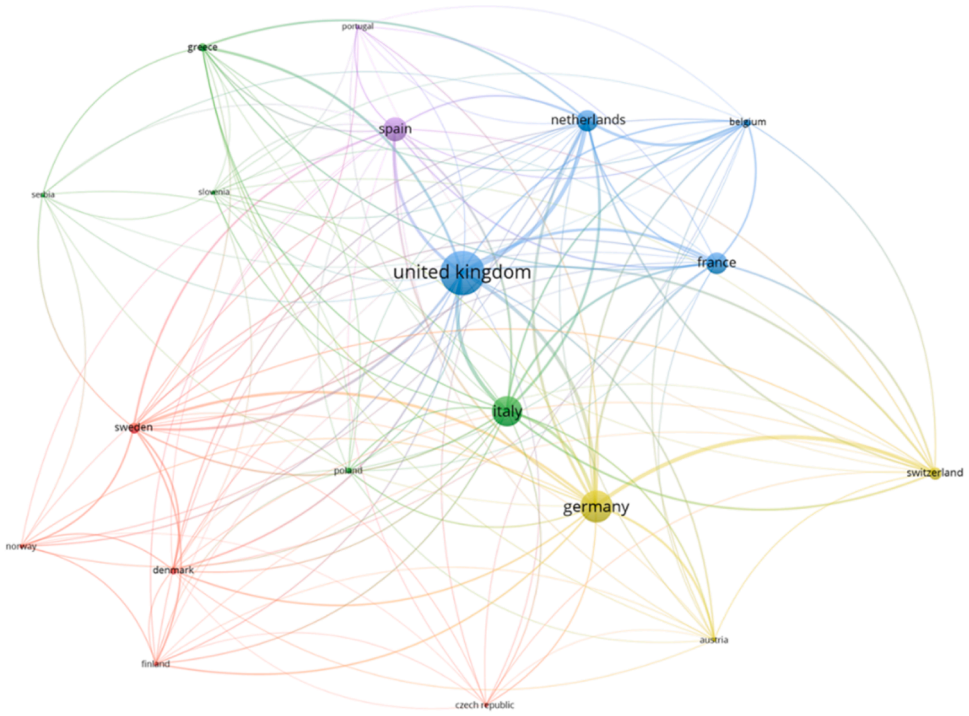

Fig. 2. Graphic depiction of the collaborations among researchers in pharmacogenetics and pharmacogenomics from different Western European countries, as attested by co-authorship. Data correspond to a Scopus search of the words pharmacogenetics OR pharmacogenomics in the title, abstract, or keywords, and the affiliation country, with no time limitation (accessed July 24, 2023). Data were analyzed by using VOSviewer (https://www.vosviewer.com/).

the Clinical Pharmacogenetics Implementation Consortium [16]. Since then, the scientific production in pharmacogenetics and pharmacogenomics in Spain has become stable, and clinical translation was greatly facilitated as Clinical Pharmacogenetics implementation Guidelines were made available to the scientific community (https://cpicpgx.org/), a good number of these being developed with the participation of Spanish experts.

In the 2010 s, several groups of specialists in Clinical Pharmacology began to implement pharmacogenetics for the care of patients in daily clinical practice [17,18]. Likewise, they planned several studies on patients to search for new biomarkers of response to drugs in more complex pathologies [19–21] and several multicentre randomized clinical trials to validate the utility of pharmacogenetic biomarkers in daily clinical practice in the Spanish national health system [22–24].

In this review, we summarize salient findings of Pharmacogenetics and Pharmacogenomics research in Spain, including basic research and examples of clinical translation at the bedside in different hospitals.

2. Examples of translational research

2.1. NSAID pharmacogenomics

Major examples of developments by Spanish groups in the pharmacogenomics of non-steroidal anti-inflammatory drugs (NSAIDs) were the identification of the pharmacogenes determining the pharmacokinetics [25,26], the adverse effects, and the modulation of potential benefits for NSAID use, mainly in the laboratory of Prof José A.G. Agundez [27]. The most relevant pharmacogenes related to NSAIDs belong to the *CYP2C* family, with *CYP2C8* and *CYP2C9* being the major genes involved in the biodisposition of ibuprofen and many other NSAIDs. Also, genetic variability in CYP2C activity is involved in adverse reactions to NSAIDs, such as gastrointestinal bleeding [28] or drug hepatotoxicity [29], with individuals with impaired metabolism being exposed to higher drug concentrations and therefore being more prone to developing adverse drug effects. Recently a Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for *CYP2C9* and NSAIDs has been published, providing therapeutic recommendations for individuals with impaired CYP2C9 enzyme activity and thus transferring pharmacogenomics information to clinical practice [30].

However, the potential of NSAID pharmacogenomics is not limited to drug pharmacokinetics or drug exposure, as it also includes the genetic variability in the drug targets, which in this case are the cyclooxygenase (COX) enzymes [31]. COX inhibition is related to the therapeutic and adverse effects of NSAIDs. Next-generation sequencing of the genes coding for the COX enzymes, namely *PTGS1* and *PTGS2*, revealed a high interindividual variability, including transcription factor binding sites [32] and nonsynonymous SNPs [33]. It has been demonstrated that individuals with altered COX activity, particularly carriers of a haplotype determined by the SNPs rs10306187 and rs10306188, are at increased risk of developing NSAID-related hypersensitivity. Such a particular haplotype leads to a functional impairment of COX1 activity, thus suggesting that individuals with decreased COX activity might be more prone to presenting adverse drug events when exposed to COX inhibitors [33]. Also, studies carried out in Spain revealed that the combination of non-synonymous SNPs in the *PTGS* genes and long-term exposure to COX inhibitors is related to an increased risk of developing drug-induced liver injury [34].

These findings raise new pharmacogenomics targets for NSAID use, based on the fact that altered response to NSAIDs might be related either to increased drug exposure (such as that related to impaired drug metabolism) or to a genetically determined low COX activity, which might sum to the inhibition caused by NSAIDs, thus amplifying the therapeutic, but also the adverse, effects. Genetic variability in drug targets is a relatively low-developed field in pharmacogenomics and it has ample room for improvement. The example with NSAIDs demonstrates that it has great potential and that it might provide key information for pharmacogenomics implementation, isolated or combined with biomarkers for pharmacokinetic or drug exposure, as well as other susceptibility factors to adverse drug reactions such as, for example, the effect of modulators of CYP2C9 activity, such as Cb5 [35], the variability in genes involved in the redox status, or patient's phenotypic factors [36].

2.2. Histamine pharmacogenomics

Histamine (2-[4-imidazole]ethylamine) is one of the most important biogenic amines and was first identified as a mediator in biological functions in the early 1900 s. The group by Prof. Elena García-Martín has provided crucial information on the genetic variability of the enzymes involved in histamine homeostasis [37]. The clinical implications are multiple since histamine is involved in the regulation of numerous pathophysiological processes including, gastric acid secretion, hypersensitivity reactions, and asthma, among others. Also, in the central nervous system, histamine has the roles of neuromodulator and classical transmitter regulating several brain functions.

Histamine homeostasis is finely regulated by three enzymes and the genes coding for these enzymes are highly polymorphic. These include the *HDC* gene, which codes for L-histidine decarboxylase (HDC, E.C. 4.1.1.22), a decarboxylase pyridoxal phosphate (PLP)-dependent enzyme that is highly specific for the substrate histidine. This is the sole enzyme involved in histamine synthesis. Two enzymes are responsible for histamine biotransformation: The histamine N-methyltransferase (HNMT, E.C. 2.1.1.8), an *S*-adenosyl-methionine (AdoMet)-dependent enzyme that catalyzes the *N*-methylation of histamine, which is the primary enzyme responsible for inactivating histamine in the brain, and the diamine oxidase (DAO; ABP1, E.C. 1.4.3.6), or amiloride-binding protein 1 (ABP1), which is responsible for scavenging extracellular histamine after mediator release, and is expressed in several human tissues [37]. Regarding histamine receptors, designated as HRH1 to HRH4, studies by Prof. García-Martín's group revealed that the genes coding for these receptors are well conserved and that genetic variability of HRH receptors is quite low, as compared to that of the genes coding for the enzymes involved in histamine homeostasis [37,38].

Concerning the *HDC* gene, Prof. Garcia-Martin's group found three novel polymorphisms in this gene, their allele frequencies and demonstrated that the increased-function *HDC* allele Glu644 in homozygosity increases the risk of developing rhinitis with a significant gene-dose effect, suggesting that increased HDC activity may play a role in rhinitis [39]. Studies on the variability of the *HNMT* gene identified a significant association with the risk of developing neurodegenerative disorders [40,41], such as Parkinson's disease (PD), with patients with increased inferred HNMT activity being at increased risk of developing PD. The association is particularly high in patients with late-onset PD, and it is consistent with the role of histamine as a neurotransmitter and the role of HNMT as the main enzyme involved in histamine metabolism in the central nervous system.

As for the *DAO* (also known as *ABP1*) gene, Prof. Garcia-Martin's group analyzed the functional impact of three common nonsynonymous polymorphisms in the *ABP1* gene [42], revealing that these SNPs cause major changes in the enzyme kinetics. Also, they described the allele frequencies and the clinical implications [43] of these amino acid substitutions related to asthma and rhinitis [44,45], hypersensitivity reactions to drugs [45,46], and migraine [47]. In addition, seeking phenotyping factors that might modulate the impact of genetic variability on histamine metabolism in vivo, they identified highly significant sex-related differences in enzyme activity [48], with women showing an average enzyme activity three times higher than men. Also, a higher interindividual variability on enzyme activity was found in women (range 1.59 to 14.0 U/L) as compared to men (range 0.90 to 4.32 U/L). Finally, they compared the variability in the genes coding for the histamine receptors *HRH1*, *HRH2,* and *HRH4* in patients with NSAID hypersensitivity and healthy individuals [49]. All these studies paved the way for the use of genomic biomarkers for histamine exposure in the

development of allergic responses and neurodegenerative disorders.

2.3. Pharmacogenetics of antipsychotics

The group originally led by Prof. Amalia Lafuente and currently by Prof. Sergi Mas and Prof. Patricia Gassó greatly contributed to the understanding of the pharmacogenetics of antipsychotics. Genetic factors play a crucial role in the antipsychotic (AP) treatment outcome. Multiple studies have reported genetic associations related to AP dosing, response, and adverse effects, and guidelines based on such associations have been developed (see, for instance, [50]). Although some commercial tests have been proposed to be used in clinical practice, randomized clinical trials are needed to demonstrate their effectiveness in reducing the conventional "trial-and-error" approaches [51]. Most pharmacogenetics studies of AP treatment are based on the hypothesis-driven candidate gene strategy. Regarding pharmacokinetics, *ABCB1,* and cytochrome P450 genotypes are among the main genes involved in AP metabolism: Among these, *CYP1A2*, *CYP2D6,* and *CYP3A4* have been extensively investigated. Significant associations reported for *CYP2D6* have led the FDA to include warnings for increased risk of developing AP-induced side effects among CYP2D6 poor metabolizers. Regarding pharmacodynamics, genes related to dopamine, serotonin, and glutamate, including those coding for receptors and metabolic enzymes for these neurotransmitters, have been widely studied. Given that D2 blockade is crucial in the APs mechanism of action, *DRD2* has been the most investigated candidate gene. Particularly, rs180498, rs2514218, and rs1079597 have been consistently associated with treatment response [51].

Most results obtained in candidate gene studies are not well replicated mainly due to the modest sample sizes in these studies, and their heterogeneity in terms of diagnosis, APs used, and treatment duration. To reduce this heterogeneity, 16 centers in Spain participated in the PEPs study (phenotype-genotype and environmental interaction; Application of a predictive model in first psychotic episodes (FEP)) that only included FEP patients with an AP treatment initiation that did not exceed 12 months [52]. Interesting associations were found between *DRD2* and extrapyramidal symptoms [53], prolactin levels [54], and metabolic traits [55]. These studies also identified other genetic associations involving candidate genes related to the pharmacodynamics of APs or the pathophysiological mechanisms of adverse events including *HTR2A*, *GRIK3*, *SLC18A2*, *NTRK2*, *ACE*, *CRN1*, *DRD3*, *FTO,* and *LEPR*. The convergent functional genomics approach that is based on the integration of multiple lines of evidence, such as gene expression data from different models including cell culture, animal and human models, was also used in these patients to identify new candidate genes, such as *EP300*, related to AP treatment [56,57]. This approach was also a clue for the group to develop a method for predicting the onset of AP-induced extrapyramidal symptoms which was patented (EP13382027.4) and transferred to the biotechnology company AB-Biotics.

The hypothesis-free genome-wide association studies (GWAS) have been also implemented in this field. The study by Yu *et al.* [58], which included one of the largest sample sizes reported so far, identified new interesting genes, such as *MEGF10*, *SLC1A1*, *PCDH7*, *CNTNAP5* and *TNIK*, which are clinically relevant and provide novel insights into the underlying AP mechanisms of action. Interestingly, results of GWAS in schizophrenia have been recently used to generate polygenic risk scores (PRS). This approach has demonstrated substantial potential to predict AP efficacy as patients with higher schizophrenia PRS tended to be non-responders to treatment [59]. Other PRS have been recently assessed to identify genetic predictors of the clinical progression of patients suffering from FEP related to AP treatment. Regarding metabolic disturbances in FEP, body mass index PRS plays a key role in determining increases in this metabolic parameter [60], and cholesterol-related PRSs have been associated with higher increases in cholesterol levels of FEP patients from the PEPs study [61].

This evidence shows that response to AP drugs is clearly a complex and polygenic trait for which pharmacogenetics research is needed to implement a more personalized treatment in patients with schizophrenia and related disorders.

2.4. Pharmacogenetics of transplantation and pediatric cancer

The Clinical Pharmacology Unit in the University and Polytechnic Hospital La Fe, in Valencia, coordinated by Prof. S.F. Aliño, began to incorporate pharmacogenetics with immunosuppression in transplantation and, later, in cancer treatment. For this purpose, a mixed panel of pharmacogenes with high evidence of association with immunosuppressants and concomitant drugs was selected. Two panels called VIP-basic (14 genes and 37 SNPs) and VIP-onco (61 genes, and 97 SNPs) were selected, based on specific reviews by Prof. Aliño's group [62–64], on the recommendations of the main drug agencies and International Consortia of Professional Societies and assuming the levels of scientific evidence established by PharmGKB for the genetic variant-pharmacological effect associations.

To guarantee the correct implementation of the pharmacogenetic analyses, a pilot study on traceability, sample flow, and final report was carried out. They observed that 50% of the patients analyzed were carriers of at least one risk variant associated with immunosuppressants with a high level of evidence, and 100% of the patients were carriers of more than one risk variant with a medium level of evidence [62–64]. Regarding concomitant therapy, the incidence was 30% for voriconazole (level 1), and omeprazole (level 2), and 10% for NSAID (level 2). The pharmacogenetic analysis report uses a table format that allows to easily and quickly view (in a single row) each of the variants with their level of evidence (using colors/icons), risk and type (pharmacokinetic, pharmacodynamic), clinical effect (gain, loss, toxicity) and recommendation (if supported). In addition, an electronic repository of protected access reports was generated.

The short-term observations in solid organ (heart, lung, kidney, liver) or hematopoietic transplant recipients show [65–67] in the early post-transplant stages that: a) genetic variants in *ABCB1* and *CYP3A5* are associated with risk for changes in plasma levels of immunosuppressants and their toxic effects; b) *ABCC2* and *SLCO1B1* variants are associated with pharmacokinetic changes of mycophenolate and nephrotoxicity of immunosuppressants; c) *NOD2/CARD15* variants are associated with heart-lung implant rejection. At 2-year follow-up, after hematopoietic transplantation, delayed neutrophil and platelet recovery were associated with *TPMT* variants, reduced survival was associated with *ABCB1* and *CYP2B6* variants, and increased incidence of Graft Versus Host Disease was associated with *ABCB1* variants. In the 12-year follow-up/prognosis of liver transplantation [67], a notable decrease in survival was found associated with *MTHFR* variants, and associations were found for increased incidence of some pathologies such as de novo cancer (*UGT1A9*), arterial hypertension (*ABCB1*), chronic nephrotoxicity (ABCB1, *ABCC2*) and *diabetes mellitus* (*ABCG2*).

Finally, the use of these mixed panels allows the identification of drug-drug interactions of clinical importance. Prof. Aliño's group described two: a) in liver transplantation [68], the interaction between tacrolimus (*CYP3A5*) and omeprazole (*CYP2C19*). When variants of both pharmacogenes are non-expressing, tacrolimus levels are increased and are associated with severe renal toxicity; b) in pediatric oncology [69], *MTHFR* variants are associated with increased survival after chemotherapy in patients with neuroblastoma carrying an altered *MYCN* gene. These and more recent observations by this group [70,71] support the interest of pharmacogenetic panels.

3. Examples of clinical implementation

3.1. Implementation of pharmacogenetics in Galicia from Galician Public Foundation of genomic medicine

The Galician Public Foundation of Genomic Medicine is a non-profit organization that provides comprehensive clinical genetic services to all hospitals within the Galician Service of Health (SERGAS) encompassing

2.6 million residents and ensuring citizens' equitable access to genetic testing (https://xenomica.sergas.gal/?idioma=es). These clinical genetic services include genetic counseling, prenatal diagnosis, oncohematology and solid cancer, hereditary diseases, pharmacogenetics, and research activities with over 40,000 patients per year.

The Pharmacogenetics Unit, led by Prof. A. Carracedo and Dr. O. Maroñas, began its activity in pharmacogenetics in 2016 and has been devoted to translating pharmacogenetics into clinical care and developing research. In line with these purposes, specific pharmacogenetic customized panels were developed. To ensure that the most relevant alleles from pharmacogenes were selected that allow the correct inference of the pharmacogenetic phenotype, a deep assessment of pharmacogenetic associations was performed and information from pharmacogenetic and population genetic databases was explored. Pharmacogenetic information from consortia, such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) and Dutch Pharmacogenetics Working Group (DPWG) together with Regulatory Agencies such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), as well as the Spanish Agency for Medicines and Health Products (AEMPS), was carefully reviewed [72]. As a result, a pharmacogenetic panel covering all clinically relevant pharmacogenes and polymorphisms was developed and validated. The analysis is performed in a customized array of 120 biomarkers and 21 pharmacogenes by using *TaqMan* probes genotyping technology (QuantStudio 12k Flex-Open Array), allowing to analyze patients in treatment with antipsychotics, antidepressants, some antineoplastics (such as fluoropyrimidines derivatives) or antiplatelet agents (such as clopidogrel), among others. The design of the panel is annually revised. However, to have enough flexibility to be able to test new biomarkers that might become important, analyses with real-time PCR single tubes are also developed, such as the case of *NUDT15* for thioguanine, included in 2020. The main clinical activity of the Pharmacogenetics Unit is developed in cancer and psychiatry, and the results report is included in the electronic clinical record of the patient.

In 2021, the Pharmacogenetics Unit started to develop a Plan for Implementation of Pharmacogenetics in Psychiatry together with SERGAS and within the Post-COVID-19 Mental Health Plan of Galicia. This initiative aims to integrate pharmacogenetics into psychiatric care for patients receiving long-acting antipsychotics, to reduce hospital admissions, treatment-related adverse effects, and to enhance effectiveness [73]. This implementation plan has been recognized with the Clinical Innovation Award in the Clinical Program category of the Spanish Society of Psychiatry in 2022. Pharmacogenetic analyses applied to clinical routine in psychiatry increased, not only for long-acting antipsychotics but also for other psycho-drugs [74–76]. It is also relevant to highlight the impressive increase in pharmacogenetic analysis of *DPYD* for fluoropyrimidines treatment, especially after EMA recommendations in 2020 [77]. Finally, it is worth mentioning that the Pharmacogenetic Unit has established collaborations worldwide to explore pharmacogenetics related to different drugs [78–82]. Recently, the Unit developed whole-genome strategies and clinical and technical guidelines applied to patients with adverse reactions to vaccines.

In conclusion, the Pharmacogenetics Unit of the Galician Public Foundation of Genomic Medicine is a novel initiative focused on translating pharmacogenetics into clinical care, as well as developing research in pharmacogenetics [72–77], and technical and clinical guides to advance in the discovery and validation of pharmacogenetic biomarkers that could be used in clinical practice.

3.2. Implementation of pharmacogenetics at Hospital Universitario de La Princesa, Madrid: PriME-PGx

The Pharmacogenetics Unit of Hospital Universitario de La Princesa led by Prof. F. Abad-Santos, began its research activity in pharmacogenetics in the year 2000 and has produced a large number of publications on pharmacogenetic biomarkers related to pharmacokinetics [83–87], safety [88,89], and efficacy in psoriasis [21], coagulation [22,90], and pain [91]. Soon, pharmacogenetics began to be applied at the care level to adjust the treatment of patients [92], showing a reduction in the incidence of adverse drug reactions [93] and in the healthcare cost [94]. Over the years, various pharmacogenetic determinations have been incorporated for healthcare activity, which are presented in chronological order: 2006 *TPMT* for thiopurines, 2008 *HLA-B:5701* for abacavir, 2011 *IFNL3* for pegylated interferon and ribavirin, 2013 *CYP2C19* for clopidogrel, 2015 *DPYD* for fluoropyrimidines, 2015 *CYP2D6* for antidepressants, antipsychotics, codeine and tramadol, 2019 *NUDT15* for thiopurines and 2020 *CYP2C9* for siponimod [18].

In the beginning, the analysis of these genes was conducted using real-time PCR for the most relevant alleles that allow the correct inference of the pharmacogenetic phenotype. Since 2019, the analysis has been performed in a customized array that uses the *TaqMan* probes genotyping technology (QuantStudio 12k Flex-Open Array). This array (the Very Important Pharmacogene Open Array panel, VIPOA) is updated annually and contains the clinically relevant genes and polymorphisms included in the clinical guidelines of the Clinical Pharmacogenetics Implementation Consortium (CPIC) [95,96], the Dutch Pharmacogenetics Working Group (DPWG) and the Spanish Society of Pharmacogenetics and Pharmacogenomics (SEFF) available at PharmGKB webpage. The current chip design contains 180 SNPs in fifty-nine genes, which includes sixteen genes that affect 25 pharmacological groups of compounds for which there are clinical practice guidelines [18].

Consequently, relevant information is obtained for each patient beyond the gene-drug pair requested by the prescribing physician. This technological change led to the launch of La Princesa University Hospital Multidisciplinary Initiative for the Implementation of Pharmacogenetics (PriME-PGx) [18], one of the first initiatives for the implementation of pharmacogenetics in Europe [97]. PriME-PGx includes two projects to provide biomarker results that could be useful to the patient in the future. On the one hand, the PROFILE project provides patients with a report based on pharmacogenetic profiles adapted to the following categories: pain unit, cardiovascular, digestive, infectious, immunosuppressive, neuropsychiatry, oncology, and complete pharmacogenetic profile. In each of these profiles, the relevant gene-drug pairs for each service or specialty are reported [18]. The report provides data on the genes and polymorphisms analyzed, patient results, and individualized recommendations for the affected drugs, and it is included in the patient's electronic medical record. In addition, if the patient carries a mutation associated with a future risk, an alert is included in the medical record to notify the prescribing physician when the medication is to be prescribed. Moreover, more complex patients are scheduled for a pharmacogenetic consultation to take a complete drug history and adjust treatment based on clinical characteristics, pharmacogenetic biomarkers, and drug interactions.

On the other hand, the GENOTRIAL project consists of the genotyping of healthy volunteers who participate in the phase I clinical trials conducted at our hospital. Thus, the relationship of pharmacogenetic markers with the pharmacokinetics or safety of the administered drug can be analyzed. Also, it provides clinically relevant results that may be useful for the subject in the future. For this reason, each volunteer is provided with a pharmacogenetic report of clinically relevant findings that can be shown to the attending physician [18].

In conclusion, PriME-PGx is a novel initiative at the national and international level, which aims to apply pharmacogenetics in clinical practice with anticipated genotyping of various groups of patients and the results made available in the clinical history.

3.3. Implementation of pharmacogenetics at Hospital Universitario de La Paz, Madrid

La Paz University Hospital (HULP) is a tertiary-care teaching hospital belonging to the Spanish National Healthcare System (NHS), with 1200

beds and serving a population of 600,000 people. The research activity of the Clinical Pharmacology Department, linked to the Pharmacology Department of Universidad Autónoma de Madrid started 20 years ago, evaluating the pharmacokinetics-pharmacogenetics relationship of some drugs, nested to bioequivalence trials [23,26,98,99] and then with the discovery and development of new biomarkers and prediction algorithms [24,100–102] and their validation in clinical trials [22,23].

In 2014 the Clinical Pharmacology Department created the Pharmacogenetics Unit to implement a strategy for pre-emptive genotyping of pharmacogenetics biomarkers associated with drug response in the clinical practice of the hospital [17]. This activity, led by Dr. A. M. Borobia, was included as an additional tool to improve drug individualization, in addition to therapeutic drug monitoring, therapeutic consultation, pharmacovigilance, and clinical toxicology programs, which are routine activities of the Department [103].

The Pharmacogenetics Unit has a multidisciplinary team with a clinical pharmacogenetics consultation, led by the Department of Clinical Pharmacology, using a personalized single nucleotide polymorphism (SNP) microarray managed at the Genetic Department, covering 180 SNPs associated with drug response (PharmArray) [104]. The current profile of services includes all the pharmacogenetic biomarkers with clinical practices guidelines or 1A evidence level in the PharmGKB Clinical Annotation (https://www.pharmgkb.org/): abacavir, voriconazole, aminoglycosides, fluoropyrimidines, irinotecan, thiopurines, tacrolimus, methotrexate, tamoxifen, antiepileptics, tricyclic antidepressants, selective serotonin reuptake inhibitors, atomoxetine, siponimod, clopidogrel, acenocoumarol, statins, opioids, NSAIDs, drugs associated with malignant hyperthermia, ivacaftor, allopurinol, ondansetron, tropisetron, and proton pump inhibitors.

The strategy for the implementation of pharmacogenetics in the clinical practice included: i) the elaboration of protocols in collaboration with the petitionary clinical services including pharmacogenetic markers relevant for drugs used for specific diseases, ii) the adoption of a pre-emptive genotyping approach in populations at risk of receiving a potential drug (i.e. voriconazole in patients with risk of aspergillosis [100]), and iii) an individualized interpretation of the pharmacogenetics results, taking into account each patient's clinical background, individual interactions, and other factors in addition to genetic information, to offer an individualized clinical recommendation.

The workflow for the management of blood samples and patient flow involves both the Clinical Pharmacology and the Genetic Department. In those cases, in which there is a specific protocol for a specific indication that has been agreed upon with the clinicians, the clinical department sends the blood samples to the Genetic Department, and a query to the Pharmacogenetics Unit is automatically created. A molecular report is generated by a molecular geneticist and submitted to the clinical pharmacologists for the elaboration of an individualized report, considering each patient's clinical record. This clinical report is sent to the treating physician through the electronic history record (EHR); If there is no previous protocol, the patient is directly referred to the Pharmacogenetics Unit where the clinical pharmacologist assesses if a pharmacogenetic test is recommended and, if so, the process would be the same as previously described [17].

The Pharmacogenetics Unit performs over 1000 pharmacogenetic studies each year and elaborates around 1000 individualized reports. Over half of the studies follow the pre-emptive genotyping approach. The most frequent petitionary services are oncology, internal medicine, dermatology, and pediatric hemato-oncology [105].

4. Concluding remarks

In this manuscript we presented an overview and a few examples of research and implementation of Pharmacogenetics and Pharmacogenomics in Spain. Because of space limitations, the examples presented here could not be exhaustive. Some additional examples include research on drug-induced liver injury, anticoagulation, and other cardiovascular drugs, or studies on pharmacogenetics implementation [100,106–113].

The development in Pharmacogenetics and Pharmacogenomics in Spain is high for a country of its size. Spanish research groups both, at the basic and the clinical levels, greatly contributed with original research to this area and made a relevant impact at the international level. The participation of Spanish researchers in international Pharmacogenetics consortia is high. For instance, in the Clinical Pharmacogenetics Implementation Consortium (https://cpicpgx.org/) there are 9 Spanish members, in PharmVar (https://www.pharmvar.org/) there are 8 Spanish members, the International Consortium for Personalised Medicine (ICPerMed) (https://www.icpermed.eu/), limited to funding organizations and ministries, has 3 Spanish members, and the Ubiquitous Pharmacogenomics Consortium (https://upgx.eu/u-pgx-consortium/), that recently presented results of a 12-gene pharmacogenetics panel, includes one Spanish research group [114].

Recently, pharmacogenetics biomarkers were included in the catalog of genetic tests of the common portfolio of services of the Spanish National Health System, as shown in Table 1. The selection of biomarkers is, obviously, similar to those prioritized by other national and international consortia and initiatives, but some differences are present, and key gene-drug pairs are missing. Still, some room for improvement exists in the Spanish pharmacogenetics and pharmacogenomics scenario. For example, the interaction between basic and clinical research is of paramount importance and this can be developed further in Spain. The combination of the skills and knowledge of basic scientists, for instance in enzymology and molecular genetics, and clinical scientists, in pharmacokinetics and assessment of drug effects, can provide more accurate and timely pharmacogenomics protocols for clinical implementation. This combination of basic and clinical researchers is well understood by the Clinical Pharmacogenomics Implementation Consortium (CPIC), which gathers multidisciplinary teams composed of basic and clinical researchers for the development of clinical practice guidelines [30,95,96]. For instance, pharmacogenomics tests assumed for years a similar effect of the *CYP2C9*2* and the *CYP2C9*3* variant alleles, despite early compelling evidence indicating that *CYP2C9*2* only causes a mild effect on enzyme activity [25]. Only after the development of CPIC guidelines assessing a differential effect of these alleles (see for instance [30]), this information was translated to the clinical practice, but many years later than expected. Another example is the differential effect of *CYP2D6* variant alleles [115], the differential effect of *NAT2* variant alleles, not translated so far to clinical practice [116], or the extremely complex analysis of *CYP2D6* structural changes [117] due to a variability that, in spite that it was described many years ago [118], has not been implemented so far by most clinical pharmacogenetics laboratories.

Financial support

None.

CRediT authorship contribution statement

Gassó Patricia: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Maroñas Olalla:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Borobia Alberto:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **García-Martín Elena:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Agundez Jose A G:** Conceptualization, Data

Table 1
Pharmacogenetics biomarkers included in the catalog of genetic tests of the Common Portfolio of Services of the Spanish National Health System (23 June 2023).

Genes	Essential variants to analyse	Drug	Disease	Indication criteria	Secondary use for other drugs
CFTR	F508del (c.1521_1523delCTT), R117H (c .350 G>A), G178R (c .532 G>A), S549R (c.1645A>C), S549N (c .1646 G>A), G551S (c .1651 G>A), G551D (c .1652 G>A), G1244E (c .3731 G>A), G1349D (c .4046 G>A), S1251N (c .3752 G>A), S1255P (c .3763 T > C)	Ivacaftor	Cystic fibrosis	Candidates for treatment with ivacaftor.	
CYP2C19	*CYP2C19*2, *3, *4* and **17*.	Atazanavir	Human immunodeficiency virus disease (HIV)	Candidates for treatment with atazanavir concomitantly with voriconazole and ritonavir.	Amitriptyline, citalopram, clomipramine, dexlansoprazole, doxepin, escitalopram, imipramine, lansoprazole, pantoprazole, sertraline, trimipramine.
		Clopidogrel	Diseases of the circulatory system	Limited to suspected lack of response to treatment and/or suspected adverse reaction to the drug.	
		Omeprazole	Gastric ulcer/duodenal ulcer	In the context of the treatment of *Helicobacter pylori*, limited to cases of failure of second and subsequent lines of treatment.	
		Voriconazole	Aspergillosis/fungemia	Prophylaxis of invasive fungal infections in high-risk allogeneic hematopoietic stem cell transplant (HSCT) recipients. Limited to suspected lack of response to treatment and/or suspected adverse reaction to the drug.	
CYP2C9	*CYP2C9*2* and **3*.	Siponimod	Multiple sclerosis	Candidates for treatment with siponimod.	Celecoxib, flurbiprofen, fluvastatin, ibuprofen, lornoxicam, meloxicam, phenytoin, piroxicam, tenoxicam.
CYP2D6	**3, *4, *5, *6, *9, *10, *17, *29, *36* and **41*, together with the determination of the number of active copies of the gene.	Eliglustat	Gaucher disease	Candidates for treatment with eliglustat.	Amitriptyline, aripiprazole, clomipramine, codeine, desipramine, doxepin, flecainide, fluvoxamine, haloperidol, hydrocodone, imipramine, metoprolol, nortriptyline, ondansetron, paroxetine, propafenone, risperidone, tamoxifen, tramadol, trimipramine, tropisetron, venlafaxine, zuclopenthixol
		Pimozide	Mental behavioural and neurodevelopmental disorders	Candidates for treatment with pimozide.	
		Tetrabenazine	Huntington's chorea	Candidates for treatment with tetrabenazine.	
DPYD	NM_000110.3(DPYD): c.1905 + 1 G>A (*2 A), c .1679 T > G (*13), c.2846 A>T, [c.1129-5923 C>G/c .1236 G>A] (HapB3)	Capecitabine	Malignant tumours	Candidates for treatments with fluoropyrimidines.	
		Fluorouracil	Malignant tumours	Candidates for treatments with fluoropyrimidines.	
		Tegafur	Malignant tumours	Candidates for treatments with fluoropyrimidines.	
G6PD	Alleles with decreased function depend on geographic location and ethnicity. Some of them are NM_001360016.2(G6PD): c .563 C>T, c .844 G>C, c.376 A>G/c .680 G>T, c.376 A>G/c .202 G>A, c.376 A>G/c .968 T > C, c.376 A>G/ c.95 A>G, c .1360 C>T o c .1376 G>T, but each case will have to be assessed individually	Rasburicase	Purine and pyrimidine metabolism disorders. Leukaemia of unspecified type. Tumour lysis syndrome	Candidates for treatment with rasburicase and high risk of having glucose-6-phosphate dehydrogenase deficiency.	
HLA-A	*HLA-A*31:01*	Carbamazepine	Disorders of the nerves, roots, and nerve plexuses. Epilepsy	Candidates for treatment with carbamazepine and at risk of severe adverse reaction: 1-Asian populations 2-Patients with a personal or family history of severe skin toxicity in the application of other drugs 3-Patients with severe adverse skin reactions after treatment with carbamazepine.	
HLA-B	*HLA-B*15:02*	Carbamazepine	Disorders of the nerves, roots, and nerve plexuses. Epilepsy	Candidates for treatment with carbamazepine, phenytoin, or oxcarbazepine and at risk of severe adverse reaction:	Flucloxacillin, lamotrigine
		Phenytoin	Epilepsy		

(*continued on next page*)

Table 1 (*continued*)

Genes	Essential variants to analyse	Drug	Disease	Indication criteria	Secondary use for other drugs
		Oxcarbazepine	Epilepsy	1-Asian populations 2-Patients with a personal or family history of severe skin toxicity in the application of other drugs. 3-Patients with severe adverse skin reactions after treatment with carbamazepine, phenytoin, or oxcarbazepine.	
HLA-B	*HLA-B*57:01*	Abacavir	Human immunodeficiency virus disease (HIV)	Candidates for treatments with abacavir.	
HLA-B	*HLA-B*58:01*	Alopurinol	Gout	Candidates for treatment with allopurinol and at risk of severe adverse reactions, especially in Asian and African populations.	
SLCO1B1	NM_006446(SLCO1B1):c .521 T > C	Simvastatin	Disorders of lipoprotein metabolism and other lipidaemia	Presence of severe side effects (rhabdomyolysis).	Atorvastatin
TPMT *NUDT15*	*TPMT*2, *3A, *3B, *3C* and **4* *NUDT15*2* and **3*	Azathioprine	Systemic autoimmune disease. Diseases of the digestive system. Malignant haematological neoplasms	Candidates for treatment with thiopurines.	
		Mercaptopurine	Malignant haematological neoplasms		
		Tioguanine	Malignant haematological neoplasms		
UGT1A1	*UGT1A1*28*	Irinotecan	Malignant tumours	Candidates for treatment with irinotecan.	Sacituzumab-govitecan

curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **Abad-Santos Francisco:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Aliño Salvador F:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

All authors declare that no financial or personal relationships with other people or organizations that could inappropriately influence (bias) this work exists.

Data Availability

No data was used for the research described in the article.

References

[1] B. Alexanderson, F. Sjoqvist, Individual differences in the pharmacokinetics of monomethylated tricyclic antidepressants: role of genetic and environmental factors and clinical importance, Ann. N. Y Acad. Sci. 179 (1971) 739–751.

[2] M. Ingelman-Sundberg, W.E. Evans, Unravelling the functional genomics of the human CYP2D6 gene locus, Pharmacogenetics 11 (7) (2001) 553–554.

[3] L. Bertilsson, M.L. Dahl, G. Tybring, Pharmacogenetics of antidepressants: clinical aspects, Acta Psychiatr. Scand. Suppl. 391 (1997) 14–21.

[4] U.A. Meyer, Molecular genetics and the future of pharmacogenetics, Pharm. Ther. 46 (3) (1990) 349–355.

[5] M. Eichelbaum, Polymorphic drug oxidation in humans, Fed. Proc. 43 (8) (1984) 2298–2302.

[6] H.J. Guchelaar, Pharmacogenetics: current status and future perspectives, Curr. Pharm. Des. 16 (2) (2010) 135.

[7] M. Pirmohamed, Pharmacogenetics and pharmacogenomics, Br. J. Clin. Pharm. 52 (4) (2001) 345–347.

[8] A.K. Daly, Pharmacogenetics of the major polymorphic metabolizing enzymes, Fundam. Clin. Pharm. 17 (1) (2003) 27–41.

[9] J. Benitez, L.L. A, J. Cobaleda, Debrisoquin oxidation polymorphism in a Spanish population, Clin. Pharm. Ther. 44 (1) (1988) 74–77.

[10] J. Benitez, et al., Clinical pharmacological evaluation of an assay kit for intoxications with tricyclic antidepressants, Ther. Drug Monit. 8 (1) (1986) 102–105.

[11] C. Nordin, et al., Plasma concentrations of nortriptyline and its 10-hydroxy metabolite in depressed patients–relationship to the debrisoquine hydroxylation metabolic ratio. Br. J. Clin. Pharm. 19 (6) (1985) 832–835.

[12] J.A. Agundez, J. Benitez, Debrisoquine polymorphism: mechanism for very rapid oxidative phenotype, Lancet 341 (8846) (1993) 689.

[13] J.A. Agundez, et al., Genetic basis for differences in debrisoquin polymorphism between a Spanish and other white populations, Clin. Pharm. Ther. 55 (4) (1994) 412–417.

[14] J.A. Agundez, et al., Prevalence of CYP2D6 gene duplication and its repercussion on the oxidative phenotype in a white population, Clin. Pharm. Ther. 57 (3) (1995) 265–269.

[15] J.A. Agundez, et al., Toward a clinical practice guide in pharmacogenomics testing for functional polymorphisms of drug-metabolizing enzymes. Gene/drug pairs and barriers perceived in Spain, Front. Genet 3 (2012) 273.

[16] M.V. Relling, T.E. Klein, CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network, Clin. Pharm. Ther. 89 (3) (2011) 464–467.

[17] A.M. Borobia, et al., Clinical implementation of pharmacogenetic testing in a hospital of the Spanish National Health System: strategy and experience over 3 years, Clin. Transl. Sci. 11 (2) (2018) 189–199.

[18] P. Zubiaur, et al., PriME-PGx: La Princesa University Hospital Multidisciplinary Initiative for the Implementation of Pharmacogenetics, J. Clin. Med. 10 (17) (2021).

[19] R. Lopez-Rodriguez, et al., Genetic variants of interferon-stimulated genes and IL-28B as host prognostic factors of response to combination treatment for chronic hepatitis C, Clin. Pharm. Ther. 90 (5) (2011) 712–721.

[20] B. Almoguera, et al., Association of common genetic variants with risperidone adverse events in a Spanish schizophrenic population, Pharm. J. 13 (2) (2013) 197–204.

[21] R. Prieto-Perez, et al., New polymorphisms associated with response to anti-TNF drugs in patients with moderate-to-severe plaque psoriasis, Pharm. J. 18 (1) (2018) 70–75.

[22] H.Y. Tong, et al., Acenocoumarol pharmacogenetic dosing algorithm versus usual care in patients with venous thromboembolism: a randomised clinical trial, J. Clin. Med 10 (13) (2021).

[23] J. Monserrat Villatoro, et al., Randomised multicentre clinical trial to evaluate voriconazole pre-emptive genotyping strategy in patients with risk of aspergillosis: vorigenipharm study protocol, BMJ Open 10 (10) (2020) e037443.

[24] A.M. Borobia, et al., An acenocoumarol dosing algorithm using clinical and pharmacogenetic data in Spanish patients with thromboembolic disease, PLoS One 7 (7) (2012) e41360.

[25] C. Martinez, et al., The effect of the cytochrome P450 CYP2C8 polymorphism on the disposition of (R)-ibuprofen enantiomer in healthy subjects, Br. J. Clin. Pharm. 59 (1) (2005) 62–69.

[26] E. Garcia-Martin, et al., Interindividual variability in ibuprofen pharmacokinetics is related to interaction of cytochrome P450 2C8 and 2C9 amino acid polymorphisms. Clin. Pharm. Ther. 76 (2) (2004) 119–127.

[27] C. Martinez, et al., Association of CYP2C9 genotypes leading to high enzyme activity and colorectal cancer risk, Carcinogenesis 22 (8) (2001) 1323–1326.
[28] G. Blanco, et al., Interaction of CYP2C8 and CYP2C9 genotypes modifies the risk for nonsteroidal anti-inflammatory drugs-related acute gastrointestinal bleeding, Pharm. Genom. 18 (1) (2008) 37–43.
[29] E. Garcia-Martin, et al., Gamma-aminobutyric acid (GABA) receptor rho (GABRR) polymorphisms and risk for essential tremor, J. Neurol. 258 (2) (2011) 203–211.
[30] K.N. Theken, et al., Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and nonsteroidal anti-inflammatory drugs, Clin. Pharm. Ther. 108 (2) (2020) 191–200.
[31] J.A. Agundez, et al., Pharmacogenomics of cyclooxygenases, Pharmacogenomics 16 (5) (2015) 501–522.
[32] J.A. Agundez, et al., Gene variants and haplotypes modifying transcription factor binding sites in the human cyclooxygenase 1 and 2 (PTGS1 and PTGS2) genes, Curr. Drug Metab. 15 (2) (2014) 182–195.
[33] E. Garcia-Martin, et al., Deep sequencing of prostaglandin-endoperoxide synthase (PTGE) genes reveals genetic susceptibility for cross-reactive hypersensitivity to NSAID, Br. J. Pharm. 178 (5) (2021) 1218–1233.
[34] M.I. Lucena, et al., Next-Generation Sequencing of PTGS Genes Reveals an Increased Frequency of Non-synonymous Variants Among Patients With NSAID-Induced Liver Injury, Front. Genet 10 (2019) 134.
[35] J. Gomez-Tabales, et al., Modulation of CYP2C9 activity and hydrogen peroxide production by cytochrome b(5), Sci. Rep. 10 (1) (2020) 15571.
[36] P. Ayuso, E. Garcia-Martin, J.A.G. Agundez, Variability of the genes involved in the cellular redox status and their implication in drug hypersensitivity reactions, Antioxid. (Basel) 10 (2) (2021).
[37] E. Garcia-Martin, et al., Histamine pharmacogenomics, Pharmacogenomics 10 (5) (2009) 867–883.
[38] E. Garcia-Martin, et al., Histamine-N-methyl transferase polymorphism and risk for migraine, Headache 48 (9) (2008) 1343–1348.
[39] G. Gervasini, et al., Variability of the L-Histidine decarboxylase gene in allergic rhinitis, Allergy 65 (12) (2010) 1576–1584.
[40] F.J. Jimenez-Jimenez, et al., Thr105Ile (rs11558538) polymorphism in the histamine N-methyltransferase (HNMT) gene and risk for Parkinson disease: a PRISMA-compliant systematic review and meta-analysis, Med. (Baltim.) 95 (27) (2016) e4147.
[41] J.A. Agundez, et al., Nonsynonymous polymorphisms of histamine-metabolising enzymes in patients with Parkinson's disease, Neuromol. Med. 10 (1) (2008) 10–16.
[42] P. Ayuso, et al., Genetic variability of human diamine oxidase: occurrence of three nonsynonymous polymorphisms and study of their effect on serum enzyme activity, Pharm. Genom. 17 (9) (2007) 687–693.
[43] G. Gervasini, et al., Genetic variability in CYP3A4 and CYP3A5 in primary liver, gastric and colorectal cancer patients, BMC Cancer 7 (2007) 118.
[44 A. Tagarro Garcia, et al., [Outbreak of measles in the population of Spanish origin in North Madrid], Anals Pediatr. (Barc.) 76 (6) (2012) 350–354.
[45] G. Amo, et al., FCERI and histamine metabolism gene variability in selective responders to NSAIDS, Front Pharm. 7 (2016) 353.
[46] E. Garcia-Martin, et al., Increased serum diamine oxidase activity in nonallergic patients with migraine, Eur. J. Clin. Invest 52 (6) (2022) e13757.
[47] E. Garcia-Martin, et al., Diamine oxidase rs10156191 and rs2052129 variants are associated with the risk for migraine, Headache 55 (2) (2015) 276–286.
[48] J.M. Ladero, et al., Glutathione S-transferases pi 1, alpha 1 and M3 genetic polymorphisms and the risk of hepatocellular carcinoma in humans, Pharmacogenomics 8 (8) (2007) 895–899.
[49] P. Ayuso, et al., Variability in histamine receptor genes HRH1, HRH2 and HRH4 in patients with hypersensitivity to NSAIDs, Pharmacogenomics 14 (15) (2013) 1871–1878.
[50] J. de Leon, et al., An international adult guideline for making clozapine titration safer by using six ancestry-based personalized dosing titrations, CRP, and clozapine levels, Pharmacopsychiatry 55 (2) (2022) 73–86.
[51] K. Yoshida, D.J. Muller, Pharmacogenetics of antipsychotic drug treatment: update and clinical implications, Mol. Neuropsychiatry 5 (Suppl 1) (2020) 1–26.
[52] M. Bernardo, et al., Modelling gene-environment interaction in first episodes of psychosis, Schizophr. Res 189 (2017) 181–189.
[53] S. Mas, et al., Pharmacogenetic study of antipsychotic induced acute extrapyramidal symptoms in a first episode psychosis cohort: role of dopamine, serotonin and glutamate candidate genes, Pharm. J. 16 (5) (2016) 439–445.
[54] P. Gasso, et al., Impact of NTRK2, DRD2 and ACE polymorphisms on prolactin levels in antipsychotic-treated patients with first-episode psychosis, J. Psychopharmacol. 32 (6) (2018) 702–710.
[55] P. Gasso, et al., Association study of candidate genes with obesity and metabolic traits in antipsychotic-treated patients with first-episode psychosis over a 2-year period, J. Psychopharmacol. 34 (5) (2020) 514–523.
[56] S. Mas, P. Gasso, A. Lafuente, Applicability of gene expression and systems biology to develop pharmacogenetic predictors; antipsychotic-induced extrapyramidal symptoms as an example, Pharmacogenomics 16 (17) (2015) 1975–1988.
[57] A. Martinez-Pinteno, et al., Identification of EP300 as a key gene involved in antipsychotic-induced metabolic dysregulation based on integrative bioinformatics analysis of multi-tissue gene expression data, Front Pharm. 12 (2021) 729474.
[58] H. Yu, et al., Five novel loci associated with antipsychotic treatment response in patients with schizophrenia: a genome-wide association study, Lancet Psychiatry 5 (4) (2018) 327–338.
[59] J.P. Zhang, et al., Schizophrenia polygenic risk score as a predictor of antipsychotic efficacy in first-episode psychosis, Am. J. Psychiatry 176 (1) (2019) 21–28.
[60] G. Muntane, et al., Polygenic risk scores enhance prediction of body mass index increase in individuals with a first episode of psychosis, Eur. Psychiatry 66 (1) (2023) e28.
[61] A.G. Segura, et al., Link between cognitive polygenic risk scores and clinical progression after a first-psychotic episode, Psychol. Med 53 (10) (2023) 4634–4647.
[62] L.E. Rojas, et al., Meta-analysis and systematic review of the effect of the donor and recipient CYP3A5 6986A>G genotype on tacrolimus dose requirements in liver transplantation, Pharm. Genom. 23 (10) (2013), 509-17.
[63] L. Rojas, et al., Effect of CYP3A5*3 on kidney transplant recipients treated with tacrolimus: a systematic review and meta-analysis of observational studies, Pharm. J. 15 (1) (2015) 38–48.
[64] G.G. Olivera, et al., Pharmacogenetics in neuroblastoma: what can already be clinically implemented and what is coming next? Int. J. Mol. Sci. 22 (18) (2021).
[65] I. Sanchez-Lazaro, et al., Association of SNPs with the efficacy and safety of immunosuppressant therapy after heart transplantation, Pharmacogenomics 16 (9) (2015) 971–979.
[66] J. Ruiz, et al., Impact of Single Nucleotide Polymorphisms (SNPs) on immunosuppressive therapy in lung transplantation, Int J. Mol. Sci. 16 (9) (2015) 20168–20182.
[67] F.D.V. Genvigir, et al., CYP3A5*3 and CYP2C8*3 variants influence exposure and clinical outcomes of tacrolimus-based therapy, Pharmacogenomics 21 (1) (2020) 7–21.
[68] L. Sendra, et al., Pharmacogene VAriants Associated with Liver Transplant in A Twelve-year Clinical Follow-up, Pharmaceutics 14 (2) (2022).
[69] V. Boso, et al., Increased hospital stay and allograft dysfunction in renal transplant recipients with Cyp2c19 AA variant in SNP rs4244285, Drug Metab. Dispos. 41 (2) (2013) 480–487.
[70] G.G. Olivera, et al., MTHFR and VDR polymorphisms improve the prognostic value of MYCN status on overall survival in neuroblastoma patients, Int J. Mol. Sci. 21 (8) (2020).
[71] A. Urtasun, et al., Personalized medicine in infant population with cancer: pharmacogenetic pilot study of polymorphisms related to toxicity and response to chemotherapy, Cancers (Basel) 15 (5) (2023).
[72] O. Maronas, et al., Progress in pharmacogenetics: consortiums and new strategies, Drug Metab. Pers. Ther. 31 (1) (2016) 17–23.
[73] F.J. Toja-Camba, et al., Review of pharmacokinetics and pharmacogenetics in atypical long-acting injectable antipsychotics, Pharmaceutics 13 (7) (2021).
[74] F. Facal, et al., Deletion of the CYP2D6 gene as a likely explanation for the serious side effects of the antipsychotic drug pimozide: a case report, Front. Pharm. 14 (2023) 1237446.
[75] G. Schoretsanitis, et al., Clozapine ultrarapid metabolism during weak induction probably exists but requires careful diagnosis. A literature review, five new cases and a proposed definition, Schizophr. Res. (2023).
[76] C.J. Ruan, et al., Exploring low clozapine C/D ratios, inverted clozapine-norclozapine ratios and undetectable concentrations as measures of non-adherence in clozapine patients: A literature review and a case series of 17 patients from 3 studies, Schizophr. Res (2023).
[77] A.R. Simoes, et al., The road so far in colorectal cancer pharmacogenomics: are we closer to individualised treatment? J. Pers. Med 10 (4) (2020).
[78] S. Blanco-Dorado, et al., Impact of CYP2C19 genotype and drug interactions on voriconazole plasma concentrations: a spain pharmacogenetic-pharmacokinetic prospective multicenter study, Pharmacotherapy 40 (1) (2020) 17–25.
[79] S. Blanco Dorado, et al., A multicentre prospective study evaluating the impact of proton-pump inhibitors omeprazole and pantoprazole on voriconazole plasma concentrations, Br. J. Clin. Pharm. 86 (8) (2020) 1661–1666.
[80] S. Blanco-Dorado, et al., An observational study of the efficacy and safety of voriconazole in a real-life clinical setting, J. Chemother. 31 (1) (2019) 49–57.
[81 L. Garcia-Quintanilla, et al., Pharmacokinetics of intravitreal Anti-VEGF drugs in age-related macular degeneration, Pharmaceutics 11 (8) (2019).
[82] O. Maronas, et al., Anti-VEGF treatment and response in age-related macular degeneration: disease's susceptibility, pharmacogenetics and pharmacokinetics, Curr. Med. Chem. 27 (4) (2020) 549–569.
[83] P. Zubiaur, et al., Influence of CYP2B6 activity score on the pharmacokinetics and safety of single dose efavirenz in healthy volunteers, Pharm. J. 20 (2) (2020) 235–245.
[84] M. Saiz-Rodriguez, et al., Effect of the most relevant CYP3A4 and CYP3A5 polymorphisms on the pharmacokinetic parameters of 10 CYP3A substrates, Biomedicines 8 (4) (2020).
[85] P. Zubiaur, et al., Effect of sex, use of pantoprazole and polymorphisms in SLC22A1, ABCB1, CES1, CYP3A5 and CYP2D6 on the pharmacokinetics and safety of dabigatran, Adv. Ther. 37 (8) (2020) 3537–3550.
[86] P. Zubiaur, et al., SLCO1B1 Phenotype and CYP3A5 polymorphism significantly affect atorvastatin bioavailability, J. Pers. Med. 11 (3) (2021).
[87] P. Soria-Chacartegui, et al., Impact of sex and genetic variation in relevant pharmacogenes on the pharmacokinetics and safety of valsartan, olmesartan and hydrochlorothiazide, Int J. Mol. Sci. 24 (20) (2023).
[88] D. Koller, et al., Metabolic effects of aripiprazole and olanzapine multiple-dose treatment in a randomised crossover clinical trial in healthy volunteers: association with pharmacogenetics, Adv. Ther. 38 (2) (2021) 1035–1054.
[89] T. Cabaleiro, et al., Paradoxical psoriasiform reactions to anti-TNFalpha drugs are associated with genetic polymorphisms in patients with psoriasis, Pharm. J. 16 (4) (2016) 336–340.

[90] M. Saiz-Rodriguez, et al., Influence of CYP2C19 phenotype on the effect of clopidogrel in patients undergoing a percutaneous neurointervention procedure, Clin. Pharm. Ther. 105 (3) (2019) 661–671.
[91] M. Saiz-Rodriguez, et al., Influence of genetic polymorphisms on the response to tramadol, ibuprofen, and the combination in patients with moderate to severe pain after dental surgery, Clin. Ther. 43 (5) (2021) e86–e102.
[92] T. Cabaleiro, et al., Utility of assessing thiopurine S-methyltransferase polymorphisms before azathioprine therapy, Curr. Drug Metab. 13 (9) (2012) 1277–1293.
[93] A. Casajus, et al., Genotype-guided prescription of azathioprine reduces the incidence of adverse drug reactions in TPMT Intermediate Metabolizers to a Similar Incidence as Normal Metabolizers, Adv. Ther. 39 (4) (2022) 1743–1753.
[94] S. Valdez-Acosta, et al., Preemptive TPMT genotyping and adherence to genotype-based therapeutic recommendations reduces the healthcare cost in patients receiving azathioprine or 6-mercaptopurine for autoimmune diseases, J. Pers. Med. 13 (8) (2023).
[95]] M.V. Relling, et al., The clinical pharmacogenetics implementation consortium: 10 years later, Clin. Pharm. Ther. 107 (1) (2020) 171–175.
[96] K.E. Caudle, et al., Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process, Curr. Drug Metab. 15 (2) (2014) 209–217.
[97] C.H. van der Wouden, et al., Implementing pharmacogenomics in europe: design and implementation strategy of the ubiquitous pharmacogenomics consortium, Clin. Pharm. Ther. 101 (3) (2017) 341–358.
[98] A.M. Borobia, et al., CYP2C9 polymorphism in five autochthonous population of the same geographic area (Spanish Pyrenees), Pharm. Res 59 (2) (2009) 107–111.
[99] A.M. Borobia, et al., Influence of sex and CYP2D6 genotype on mirtazapine disposition, evaluated in Spanish healthy volunteers, Pharm. Res 59 (6) (2009) 393–398.
[100] I. Garcia-Garcia, et al., Experience of a strategy including CYP2C19 preemptive genotyping followed by therapeutic drug monitoring of voriconazole in patients undergoing allogenic hematopoietic stem cell transplantation, Front Pharm. 12 (2021) 717932.
[101] A.J. Carcas, et al., Efficiency and effectiveness of the use of an acenocoumarol pharmacogenetic dosing algorithm versus usual care in patients with venous thromboembolic disease initiating oral anticoagulation: study protocol for a randomized controlled trial, Trials 13 (2012) 239.
[102] H.Y. Tong, et al., A new pharmacogenetic algorithm to predict the most appropriate dosage of acenocoumarol for stable anticoagulation in a mixed spanish population, PLoS One 11 (3) (2016) e0150456.
[103] E. Ramirez, et al., A pharmacovigilance program from laboratory signals for the detection and reporting of serious adverse drug reactions in hospitalized patients, Clin. Pharm. Ther. 87 (1) (2010) 74–86.
[104] R. Rosas-Alonso, et al., Analytical validation of a laboratory-development multigene pharmacogenetic assay, Pharm. Genom. 31 (8) (2021) 177–184.
[105] S. Stewart, et al., Advancing pharmacogenetic testing in a tertiary hospital: a retrospective analysis after 10 years of activity, Front. Pharm. 14 (2023) 1292416.
[106] X. Garcia-Gonzalez, et al., Clinical implementation of pharmacogenetics, Drug Metab. Pers. Ther. 31 (1) (2016) 9–16.
[107] G. Olivera, et al., Pharmacogenetics implementation in the clinics: information and guidelines for germline variants, Cancer Drug Resist 2 (1) (2019) 53–68.
[108] X. Garcia-Gonzalez, S. Salvador-Martin, Pharmacogenetics to avoid adverse reactions in cardiology: ready for implementation? J. Pers. Med. 11 (11) (2021).
[109] R.J. Andrade, et al., Pharmacogenomics in drug induced liver injury, Curr. Drug Metab. 10 (9) (2009) 956–970.
[110] M.I. Lucena, et al., Glutathione S-transferase m1 and t1 null genotypes increase susceptibility to idiosyncratic drug-induced liver injury, Hepatology 48 (2) (2008) 588–596.
[111] M.I. Lucena, et al., Mitochondrial superoxide dismutase and glutathione peroxidase in idiosyncratic drug-induced liver injury, Hepatology 52 (1) (2010) 303–312.
[112] P. Nicoletti, et al., Shared genetic risk factors across carbamazepine-induced hypersensitivity reactions, Clin. Pharm. Ther. 106 (5) (2019) 1028–1036.
[113] L.L. A, et al., Clinical implementation of pharmacogenetics and personalized drug prescription based on e-health: the MedeA initiative, Drug Metab. Pers. Ther. 35 (3) (2020).
[114] J.J. Swen, et al., A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study, Lancet 401 (10374) (2023) 347–356.
[115] A. Gaedigk, et al., The CYP2D6 activity score: translating genotype information into a qualitative measure of phenotype, Clin. Pharm. Ther. 83 (2) (2008) 234–242.
[116] J.D. Ruiz, et al., The differential effect of NAT2 variant alleles permits refinement in phenotype inference and identifies a very slow acetylation genotype, PLoS One 7 (9) (2012) e44629.
[117] A.J. Turner, et al., PharmVar tutorial on CYP2D6 structural variation testing and recommendations on reporting, Clin. Pharm. Ther. (2023).
[118] M.C. Ledesma, J.A. Agundez, Identification of subtypes of CYP2D gene rearrangements among carriers of CYP2D6 gene deletion and duplication, Clin. Chem. 51 (6) (2005) 939–943.