Farmacia Hospitalaria 48 (2024) TS5–TS12

Farmacia HOSPITALARIA
Órgano oficial de expresión científica de la Sociedad Española de Farmacia Hospitalaria
www.elsevier.es/farmaciahospitalaria

Review

[Translated article] Application of pharmacogenetic/pharmacogenomic data to personalise treatment in routine clinical practice. A narrative review

Antonio Sánchez Pozo[a,*] and Almudena Montero Gómez[b]

[a] Departamento de Bioquímica y Biología Molecular 2, Facultad de Farmacia, Universidad de Granada, Granada, Spain
[b] Farmacia Comunitaria, Granada, Spain

ARTICLE INFO

Article history:
Received 18 July 2023
Accepted 25 September 2023

Keywords:
Pharmacogenetics
Pharmacogenomic variants
Precision medicine

ABSTRACT

Objective: The aim of this article was to perform a narrative review of how pharmacogenetics and pharmacogenomics is being applied in the clinics, especially in Spain.
Method: Publications and websites of major interest have been reviewed.
Results: Pharmacogenes and variants used in several hospitals, available methodologies, and the implementation process are discussed.
© 2023 Sociedad Española de Farmacia Hospitalaria (S.E.F.H). Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Aplicación de datos farmacogenéticos/farmacogenómicos para personalizar el tratamiento en la práctica clínica habitual. Revisión narrativa

Palabras claves:
Farmacogenética
Variantes Farmacogenómicas
Medicina de Precisión

RESUMEN

Objetivo: El objetivo de este artículo ha sido realizar una revisión narrativa de cómo se está aplicando la farmacogenética y la farmacogenómica en la clínica, especialmente en España.
Método: Se han revisado las publicaciones y sitios web de mayor interés.
Resultados: Se discuten los farmacogenes y variantes en uso en varios centros hospitalarios, las metodologías empleadas y el proceso de implementación.
© 2023 Sociedad Española de Farmacia Hospitalaria (S.E.F.H). Publicado por Elsevier España, S.L.U. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

Thanks to scientific and technological progress, identifying and applying the most effective therapeutic strategy for each patient appears to be within reach and remains the goal of most healthcare systems.[1,2] Thus, the concept of precision medicine has emerged as the identification and application of the most effective therapeutic, diagnostic, and preventive strategy for each patient or population subgroup, taking into account genetic information and the influence of the environment.[3] From the perspective of pharmaceutical practice, this concept involves the assessment of genomics, environmental exposure, lifestyle, and the analysis of other unique patient or disease characteristics in order to guide drug selection and dosing.[4,5] In both cases, the focus is on genes or genomes, where genomes are understood as the combination of genes and other genetic elements rather than just the sum total of genes. This focus gives rise to pharmacogenetics and pharmacogenomics. Hereafter, we use the abbreviation PGx to refer to them interchangeably, as their objectives are essentially the same.

The implementation of PGx is expected to be hugely influential in modern society, where prescription drug use is very widespread.[6] On the one hand, PGx implementation can help prevent adverse effects that require attention and, in many cases, hospitalisation; on the other hand, it can help select treatments and eliminate those that are ineffective. By genotyping the population, PGx can also be used to predict treatment.[7] In fact, it is relatively common for individuals to possess genetic variants associated with PGx and to be exposed to multiple drugs

DOI of original article: https://doi.org/10.1016/j.farma.2023.09.011.
* Corresponding author.
E-mail address: sanchezp@go.ugr.es (A. Sánchez Pozo).

https://doi.org/10.1016/j.farma.2024.02.009
1130-6343/© 2023 Sociedad Española de Farmacia Hospitalaria (S.E.F.H). Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

over their lifetime, either serially or concurrently. Thus, PGx could help prevent adverse effects related to polypharmacotherapy.

Given this background, PGx implementation should be widespread; however, it appears that this is not the case. Therefore, we considered that it would be of interest to determine how PGx is applied in routine clinical practice in Spain (genes, variants, and methods) and the elements involved in its implementation.

Methods

Several resources were used to conduct this review: (1) The literature: A non-systematic review of the last 10 years of PubMed, WOS. The following terms were used as search terms: "Farmacogenética", "Farmacogenómica", "Medicina de Precisión", "Medicina Personalizada", "Farmacoterapia de Precisión", and "Farmacoterapia Personalizada", as well as their English translations: "Pharmacogenetics", "Pharmacogenomics", "Precision Medicine", "Personalised Medicine", "Precision Pharmacotherapy", and "Personalised Pharamacotherapy"; (2) Databases: The Pharmacogenomics Knowledge Base (PharmGKB),[8] Pharmacogene Variation (PharmVar),[9] and ClinVar.[10] PharmGKB contains information on pharmacogenes that have been approved by the US Food and Drug Administration (FDA),[11,12] European Medicines Agency (EMA),[13] Swiss Agency of Therapeutic Products (Swissmedic),[14] the Japanese Pharmaceuticals and Medical Devices Agency (PMDA),[15] and Health Canada (Santé Canada) (HCSC).[16] PharmVar mainly contains CYP450 variants. ClinVar contains pharmacogenes and other biomarkers and is the reference for genotype–phenotype relationships in humans; (3) Clinical guidelines: From the American perspective, the Clinical Pharmacogenetics Implementation Consortium (CPIC)[17] (cpicpgx.org), and from the European perspective, the Dutch Pharmacogenetics Working Group (DPWG)[18–22]; and (4) Spanish institutions and organisations: Consejo General de Colegios de Farmacéuticos (https://www.farmaceuticos.com/), Sociedad Española de Farmacia Hospitalaria (https://www.sefh.es/), Sociedad Española de Farmacogenética y Farmacogenómica (https://seff.es/), Sociedad Española de Farmacia Clínica, Familiar y Comunitaria (https://www.sefac.org/).

Results

Genes, variants, and methods

The pharmacogenes and methods employed are very similar in all the countries analysed. Table 1 shows the most commonly employed pharmacogenes. The table includes two Spanish examples because of the availability of detailed information. In total, 16% of the pharmacogenes analysed are transport proteins, 39% are metabolism proteins, and 45% are therapeutic targets. Thus, 55% of the pharmacogenes are bioavailability pharmacogenes (transport and metabolism) and 45% are therapeutic targets. The treatments involved show that the main therapeutic areas are antitumoral (23%), neurological (18%), immunosuppressant (11%), antiretroviral (10%), anticoagulant (8%), antihypercholesterolemic (8%), antidiabetic (8%), and biological (5%). These results are consistent with those depicted in Fig. 1 for services which offer PGx.

The number of variants analysed per gene is relatively small, and in most cases is limited to one. The "rs" reference numbers are shown in Table 1, allowing access to the description of each variant in the dbSNP database[26] (https://www.ncbi.nlm.nih.gov/snp).

The main analytical method used is PCR and, to a lesser extent, arrays (results not shown). In the analysis of arrays, *ad hoc* variant panels are mainly used in Spain, whereas commercially available fixed panels are in wide use in other countries. Next-Generation Sequencing (NGS) is rarely used, except in research settings. Two types of sequencing are used: Whole Exome Sequencing (WES) analyses around 1%–2% of the genome and is the most common method; and Wide Genome Sequencing (WGS) analyses the entire genome. A unique aspect of NGS is the number of reads or fragments into which the DNA is divided. These are sequenced simultaneously (bulk sequencing) and then sorted to obtain the sequence of the sample.[28] The most commonly used NGS is Long-Read Sequencing (LRS) with reads of up to 45 000.

Implementation of pharmacogenetics and pharmacogenomics

The implementation of PGx in hospital settings is widespread, whereas it remains limited in the community setting. This situation is similar in other countries. In Spanish hospitals, pharmacogenetics units have been set up to meet the demands of different clinical areas, especially oncohematology (Fig. 1).[27] In community pharmacies, the implementation of PGx is at an early stage and is very uneven. Unlike the situation in hospitals, there appears to be a lack of infrastructure and testing is outsourced to specialised laboratories.

PGx is being developed within the framework of specific programs or projects. In other countries, development is at its most advanced in the United States, with initiatives such as the Cleveland Clinic's Personalised Medication Program, the CLIPMERGE PGx Program, the eMERGE-PGx initiative, IGNITE, INGENIOUS, the 1200 Patients Project, and PREDICT.[29,30] In Europe, the Netherlands has gone furthest in developing PGx. In fact, this country was the first to publish clinical guidelines (by the DPWG) and develop systems in which prospective data on a set of key pharmacogenes are collected and included in patients' electronic medical records.[31] In Spain, noteworthy programs include those conducted by the Instituto de Salud Carlos III,[25] la Sociedad Española de Farmacogenética y Farmacogenómica,[32] Hospital de la Princesa,[24] and the MedeA Project.[33]

In the Spanish autonomous communities, PGx development remains uneven[34] (see Fig. 2). An analysis of the key elements of implementation shows that the most important factor is the existence of government plans and strategies, followed by public–private collaboration and training. The existence of a critical mass of well-trained PGx specialists and infrastructure is much less influential.

PGx has evolved from the creation of specific units in hospitals to solve specific clinical problems to the study of panels or mass sequencing of population groups in centralised laboratories at regional and national levels. In this sense, a noteworthy initiative is the Collaborative Spanish Variability Server (CSVS),[35] which is a database that has collected genomes and exomes of individuals allowing us to determine the prevalence of pharmacogenomic variants in the Spanish population.

Discussion

The number of pharmacogenes in use is relatively low compared to the number of genes considered useful or actionable pharmacogenes (284 genes associated with pharmacokinetics and 771 genes associated with pharmacodynamics).[17–22] The number of variants analysed also shows a similar discrepancy, which seems to be due to 2 main factors: biological significance and methods.

Regarding biological significance, 2 pharmacogenetic categories can be distinguished: those affecting bioavailability and those affecting therapeutic targets. The biological significance of the first group is evident, as these pharmacogenes have specific roles in drug absorption, metabolism, distribution, and elimination, and are therefore typically included in most protocols. However, the proteins involved in bioavailability have broad substrate specificity and are applicable to multiple drugs, allowing the same panels to be used in a variety of clinical situations. It should be noted that many of the proteins involved are inducible; thus, if a drug is taken with an inducing agent (e.g., alcohol or another drug) adverse effects may occur as a result of variations in protein levels. Furthermore, it should be considered that both inducibility and substrate specificity can have relevant effects in polymedicated patients.

In contrast, the biological significance of the second group is less clear, so it is not surprising that many pharmacogenes are proposed,

Table 1
Pharmacogenes employed in projects and initiatives in Spain and other countries.

CPIC + DPWG	Sanford chip	PriME-PGx	La Paz	rsID (variants)	Protein family	Function	Treatments involved
		ABCB1	ABCB1	rs2032582; rs1045642; rs3213619; rs1128503;	ATP Binding Cassette	T	Immunosuppressants and antiplatelet agents
			ABCC2	rs717620; rs56296335; rs3740066; rs56199535; rs56220353;	ATP Binding Cassette	T	Antiretrovirals
		ABCG2	ABCG2	rs2231142; rs2273697; rs72552713;	ATP Binding Cassette	T	Statins, methotrexate, imatinib (tyrosine kinase inhibitor)
			APOE	rs7412	Apolipoproteins (chaperones)	D	Anticoagulants, pravastatin
CACNA1S				rs1800559; rs772226819;	Dihydropyridine receptor	D	Statins
		COMT	COMT	rs4680	Catechol-O-methyltransferase	M	Catecholamines and derivatives
CFTR			CFTR	rs75527207; rs113993960; rs199826652; rs267606723; rs193922525; rs80282562; rs121909013; rs74503330; rs12190909041; rs121908755; rs121909005; rs121908757;	Cystic fibrosis transmembrane conductance regulator	D	Ivacaftor
		CYP1A2		rs2069514; rs762551; rs2470890;	Cytochrome P450	M	Phenacetin, caffeine, clozapine, tacrine, propranolol
		CYP2A6		rs28399433	Cytochrome P450	M	Letrozole, tegafur, coumarins, valproic, methoxyfluorane, disulfiram, halothane, fadrozol
CYP2B6		CYP2B6		rs374527407; rs3211371; rs4803419; rs2279343; rs34223104; rs28399499	Cytochrome P450	M	Artemisinin, bupropion, cyclophosphamide, efavirenz, ketamine, methadone
CYP2C19	CYP2C19	CYP2C19	CYP2C19	rs4244285; rs4986893; rs12248560; rs28399504; rs56337013; rs72552267; rs72558186; rs41291556; rs267606723; rs19393922525; rs80282562; rs121909013; rs74503330; rs12190909041; rs121908755; rs121909005; rs121908757;	Cytochrome P450	M	Antifungals and antiplatelet agents
		CYP2C8	CYP2C8	Rs11572080; rs10509681; rs1058930; rs11572103;	Cytochrome P450	M	Paclitaxel, psychotropics, oral antidiabetics
CYP2C9	CYP2C9	CYP2C9	CYP2C9	rs1799853; rs1057910;	Cytochrome P450	M	Psychotropics, anticonvulsants
CYP2D6	CYP2D6	CYP2D6	CYP2D6	rs1080985; rs28371725; rs35742686; rs3892097; rs5030655; rs5030865; rs5030867; rs5030656; rs1065852; rs1058164; rs1135840; rs16947; rs28371706; rs61736512; rs769258	Cytochrome P450	M	Psychotropics, antinausea opioids (ondansetron)
		CYP3A4	CYP3A4	rs55785340; rs4646438;	Cytochrome P450	M	Immunosuppressants
CYP3A5	CYP3A5	CYP3A5	CYP3A5	rs776746; rs55965422; rs10264272; rs41303343; rs41279854	Cytochrome P450	M	Tacrolimus
CYP4F2	CYP4F2	CYP4F2	CYP4F2	rs2108622;	Cytochrome P450	M	Anticoagulants
DPYD	DPYD	DPYD	DPYD	rs3918290; rs55886062; rs67376798; rs1801159; rs1801265;	Dihydropyrimidine dehydrogenase	M	Fluoropyrimidines (5FU)
		ERCC1	ERCC1	rs11615; rs3212986	Endonuclease excision repair	D	Cisplatin
		EPHX1	EPHX1	rs1051740	Endonuclease excision repair	M	Cisplatin
			FCGR2A	rs1801274;	Epoxide hydrolase	D	Immunotherapy
G6PD				rs782669677	Glucose-6-phosphate dehydrogenase	M	Primaquine
		HLA-A3101		rs1061235	Major histocompatibility complex	D	Carbamazepine, oxcarbazepine, lamotrigine, phenytoin
HLA-B				rs144012689	Major histocompatibility complex	D	Carbamazepine, oxcarbazepine, lamotrigine, phenytoin
		HCP5		rs2395029	Major histocompatibility complex	D	Retrovirus
			HTR2A	rs6311	5-hydroxytryptamine receptor	D	Psychotropics. Serotonin 5-HT2A antagonists
IFLN3	IFLN3			rs4803217	Interferon	D	Hepatitis C
IFLN4				rs469415590;	Interferon	D	Hepatitis C
			IL10	rs1800896 rs1800872; rs1800871	Cytokine	D	Anti-inflammatory immunotherapy
			IL23R	rs7517847; rs10489629; rs11465804; rs1343151	Cytokine receptor	D	Biological therapy
		IL28B		rs12979860	Cytokine	D	Interferon. Ribaviria

(continued on next page)

Table 1 (*continued*)

CPIC + DPWG	Sanford chip	PriME-PGx	La Paz	rsID (variants)	Protein family	Function	Treatments involved
			KCNJ6	rs2070995	Potassium channel	D	Methadone
		MTHFR	MTHFR	rs1801133; rs4846051; rs1801131	Methylene tetrahydrofolate reductase	M	Methotrexate
NUDT15		NUDT15		rs116855232	Nucleotide hydrolase	M	Thiopurines
		OPRM1		rs1799971	mu-opioid receptor	D	Antidepressants
			BY	rs1057868; rs2868177	Cytochrome P450	M	Immunosuppressants
		RARG		rs2229774	Retinoic acid receptor gamma	D	Doxorubicin
RYR1				rs118192172	Receptor ryanodine	D	Statins
			SLC15A2	rs2293616; rs2257212; rs1143671; rs1143672	H+/peptide transporter	T	Metformin
		SLC22A1	SLC22A1	rs72552763; rs55918055; rs36103319; rs34059508; rs628031; rs4646277; rs2282143; rs4646278; rs12208357	Organic cation transporter	T	Tramadol, metformin
			SLC22A2	rs316019; rs8177516; rs8177517; rs8177507; rs8177504	Organic cation transporter	T	Fampridine, metformin
			SLC22A6	rs11568626	Organic cation transporter	T	Acyclovir, zidovudine, didanosine, zalcitabine, lamivudine, stavudine, trifluridine, cidofovir, adefovir, tenofovir
		SLC28A3		rs7853758	Nucleoside transporter	T	Thiopurines
SLCO1B1	SLCO1B1	SLCO1B1	SLCO1B1	rs4149056; rs2306283; rs56101265; rs72559745; rs56061388; rs55901008; rs59502379; rs56199088; rs55737008; rs4149015	Organic anion transporter	T	Statins, irinotecan, oral antidiabetics, oestrogens
		TBL1Y		rs768983	Transducin beta	D	Biologic therapies
			TLR2	rs4696480; rs11938228	Toll Receptors	D	Immunotherapies
			TLR9	rs352139	Toll Receptors	D	Immunotherapies
			TNF	rs1800629	Tumour necrosis factor	D	Immunotherapies
			TP53	rs1042522	Tumour suppressor	D	Cisplatin
TPMT	TPMT	TPMT	TPMT	rs1800460; rs1800462; rs1142345; rs1800584	Thiopurine methyltransferase	M	Thioguanines. 6-mercaptopurine and azathioprine
UGT1A1			UGT1A1	rs887829; rs4148323; rs34993780; rs35350960; rs55750087; rs4124874	UDP-glucuronosyl transferase	M	Irinotecan. Acetaminophen, carvedilol, etoposide, lamotrigine. Simvastatin
		UGT1A4		rs2011425	UDP-glucuronosyl transferase	M	Irinotecan, paracetamol, carvedilol, etoposide, lamotrigine. Simvastatin
			UGT2B7	rs7438135	UDP-glucuronosyl transferase	M	Morphine, mycophenolate
		UGT2B15		rs1902023	UDP-glucuronosyl transferase	M	Benzodiazepines
VKORC1	VKORC1	VKORC1	VKORC1	rs9934438	Vitamin K epoxide reductase	D	Anticoagulants. Warfarin and acenocoumarol
		XPC	XPC	rs2228001	DNA repair protein	D	Cisplatin
		XRCC1	XRCC1	rs25487	DNA repair protein	D	Cisplatin, PPAR inhibitors (olaparib, niraparib, rucaparib)

CPIC, Clinical Pharmacogenetics Implementation Consortium[17]; D, Target; DPWG, Dutch Pharmacogenomic Working Group[18–22]; Sanford chip[23]; PriME-PGx, Hospital de la Princesa[24]; La Paz; Hospital de la Paz[25]; M, metabolism; rsID, reference SNP cluster identification number, variant identification number in the dbSNP[26]; T, transport.

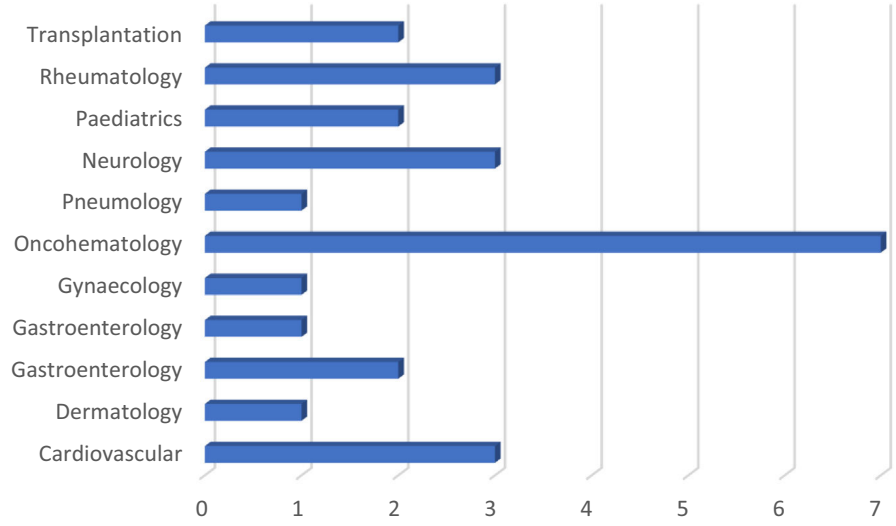

Fig. 1. Implementation of PGx by clinical area (Spain). Numbers represent the number of hospitals offering PGx services. Data obtained from the SEFH.[27]

but few are selected. In principle, the therapeutic target should be the protein responsible for the problem being addressed. Nevertheless, in most cases, the cause of the problem is an imbalance in the biological system, involving multiple proteins and the effect of the environment on them. In all cases, we are dealing with multifactorial problems. An example of this situation is depicted in Fig. 3, showing the network of factors and interactions in the case of sickle cell anaemia. As can be seen, abnormal HbS, which is the main cause of the problem, can be affected by other modifying proteins, environmental influences, and the physiological response of the individual. In this case, all of these elements should be analysed, because they give rise to different clinical phenotypes that can be treated individually; however, in practice, they are usually excluded if the effect of any of these factors is modest. Another reason why some targets are not used is that, in many cases, they have been identified as statistical associations rather than functional ones, making it unclear how they are affected. Finally, the environment can have as much impact as genes on protein function; for example, proteins may behave differently under varying pH levels. In other words, genetic studies alone do not provide a definitive basis for therapeutic decision-making. A comprehensive assessment of biological systems can be provided by analysing the metabolome, which represents the outcomes of protein action and environmental effects. In this sense, it is becoming increasingly common to include metabolite analysis alongside genetic analysis.

Some possible variants are not always analysed, which poses some level of risk from a methodological point of view. However, it is reasonable to use arrays with a limited number of genomic variants and to reserve sequencing for special cases. The concept of special cases refers to rare variants and structural variants; arrays, however, neither detect them nor allow for haplotype phasing. Rare variants can have a greater impact on gene function and expression, exhibit greater population specificity, and play relevant roles in the genetics of complex diseases.[36] Structural variants refer to deletions, duplications, insertions, inversions, and translocations, as well as complex rearrangements, all of which are very common in PGx. Regarding phasing, it should borne in mind that although the genome is often discussed as a singular entity,

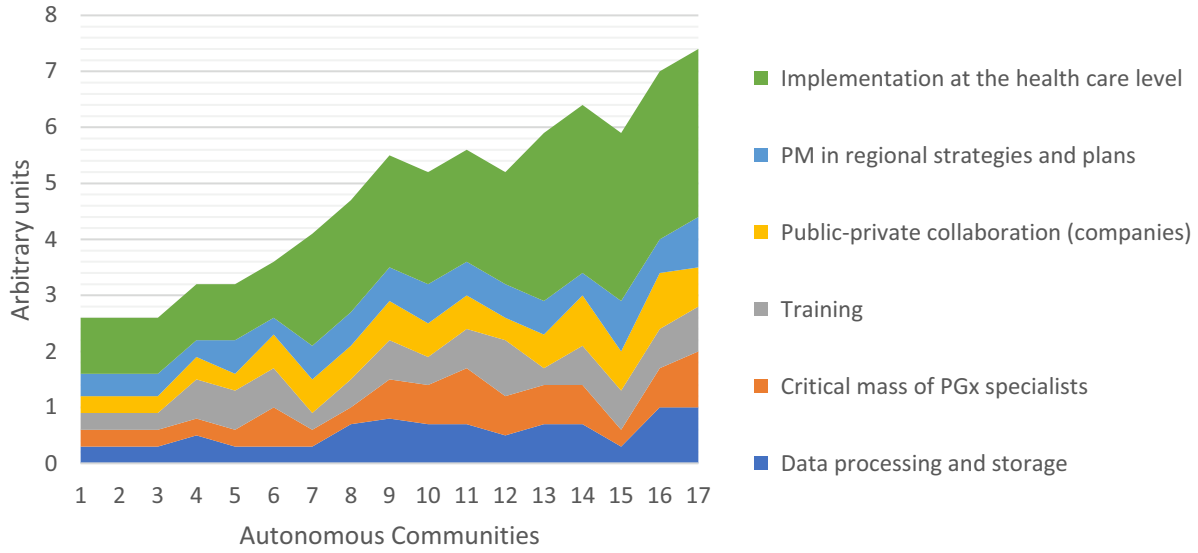

Fig. 2. Precision medicine in Spain and key elements in its development. Data obtained from the Roche report.[34] 1) Cantabria, 2) Castilla La Mancha, 3) Canary Islands, 4) Aragon, 5) La Rioja, 6) Principality of Asturias, 7) Balearic Islands, 8) Extremadura, 9) Community of Valencia, 10) Navarra, 11) Madrid, 12) Region of Murcia, 13) Castilla y León, 14) Galicia, 15) Basque Country, 16) Andalusia, and 17) Catalonia. PGx, pharmacogenetics/pharmacogenomics; PM, personalised medicine.

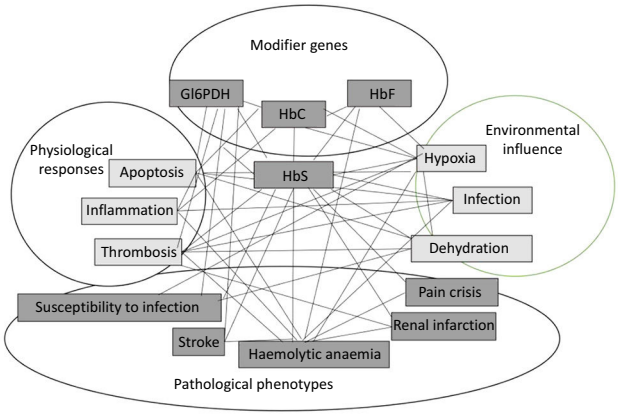

Fig. 3. Biological factors and interactions determining the clinical phenotype in sickle cell disease. HbS, sickle haemoglobin; HbF, foetal haemoglobin; HbC, haemoglobin C; Gl6PDH, glucose-6 phosphate dehydrogenase.

each person actually has a dual chromosomal endowment. The position of variants on one or the other chromosome can lead to differences in the response to drugs such as alpelisib.[37]

The predominant sequencing method is Whole Exome Sequencing (WES), which does not analyse introns. PGx has detected variants of interest in introns. On the other hand, Long Read Sequencing (LRS) is gaining momentum due to the advantage of longer read fragments, which contribute to a reduction in sequencing errors. These errors occur because DNA contains numerous similar sequences. Consequently, when using short reads, multiple alternatives can arise. In PGx, LRS is the preferred choice to study variants in complex genes such as CYP2D6 or HLA.

Implementation of pharmacogenetics/pharmacogenomics

PGx has been implemented in hospitals, but could also be implemented at all levels of the healthcare system. In fact, much of PGx is focused on outpatient drugs, such as antidiabetics, statins, and so on. Cavallari et al have outlined a set of specific elements that should be considered when establishing a PGx service.[38] These elements include patient selection, analytical genotyping procedures, computer systems, staff training, and quality control. Thus, hospitals are the preferred location for PGx implementation due to their operational facilities. There is also a historical reason for this situation: the majority of the initiatives have emerged from research projects, most of which have been hospital-based. Further PGx development is likely to occur mainly in out-of-hospital settings, and the increasing use of Internet-based gene panels may contribute to this trend. In this regard, the FDA has approved direct-to-consumers (DTC) genetic test kits, which assess risk markers for cancer (BRCA 1 and 2) and other diseases (G6PDH). Many of these tests can be done without prescription, and so there is a clear need to inform people with community pharmacies playing a key role.

However, despite significant advances in knowledge, it is striking that the implementation of PGx has been so slow, both in Spain and in other countries.[39] The reasons given for this situation include a certain level of scepticism, technical difficulties, the lack of specialists, and budget constraints.[31,40] Critics highlight the lack of clarity concerning pharmacogenes. Furthermore, genotyping tests and registration processes often lack standardisation. In addition, recognition by drug agencies, which employ varying different criteria, is relevant to PGx implementation. In Spain, at least those medicines for which the Spanish Agency of Medicines and Medical Devices and the EMA include PGx analysis in their data sheets should be included. Regarding technical difficulties, the issues primarily stem from managing the results rather than from the analyses themselves.[41] Thus, the analysis of a vast amount of data to provide a solution necessitates reliable mathematical algorithms. This aspect has significantly improved with the evolution of artificial intelligence and the substantial increase in computational capacity, thus enabling the rapid identification and application of solutions. However, this aspect remains a challenge because many such databases lack structure and interoperability, rendering their integration nearly impossible. The analytical aspect has transitioned from the early, almost handcrafted techniques to today's easily applicable automated methods. Finding a laboratory is not difficult and, currently, the SEFF is drawing up a map of laboratories in Spain. In other countries, the availability of genetic testing is very widespread and can be consulted in the Genetic Testing Registry database.[42] The number of specialists is gradually increasing and costs are steadily decreasing.

The implementation of PGx has paralleled progress in precision medicine, both in Spain and in other countries. Government plans and strategies have significantly shaped the development of precision medicine in Spain. For example, the Spanish strategy for personalised medicine was launched in 2020. Governments are investing heavily, especially in infrastructures such as the Spanish IMPaCT program.[43] Another key aspect is collaboration between the public and private sectors. In the biomedical field, such collaboration has stemmed from government programs and the keen interest of private companies, which have recognised this field as a good business opportunity. Consequently, this synergy has contributed to the remarkable growth of biotech companies in Spain (https://www.asebio.com/en). This aspect, among others, has led to an increase in the use of biotechnological treatments and the associated increase in costs, which contrasts with the expected reduction following the implementation of PGx. Some authors have suggested that this trend could lead to social inequalities by limiting access to medicines for people in lower socioeconomic groups.[44]

PGx training is of particular concern as a critical mass of well-trained PGx specialists is needed for its implementation to become widespread. As mentioned, some biomarkers have strong scientific and clinical support, whereas others are merely statistical associations that have been proven to be misleading and to have clinical implications. Discriminating between them requires well-trained specialists. In both pharmacy and medicine, undergraduate training in PGx is very scarce and postgraduate training does not include PGx as a speciality. However, courses do exist, some of which are free of charge, such as those offered by the COPHELA consortium.[45] The current trend is to form multidisciplinary teams in which pharmacists, with their training in pharmacokinetics and pharmacodynamics, should play a key role. In relation to PGx, pharmacists' responsibilities include promoting the optimal use and timing of PGx tests, interpreting PGx test results, and educating healthcare professionals, patients, and the general public about the field of pharmacogenomics.[46,47] Setting up such teams in hospitals is straightforward and improving with the creation of translational medicine units. Although this aspect can be challenging in community pharmacy, it is not insurmountable, thanks to information and communication technology.

The concept of precision medicine and PGx have evolved simultaneously.[44] Initially, the concept was captured by the term personalised medicine (i.e., where each person receives the most effective treatment while avoiding adverse effects). Subsequently, the concept was referred to as precision medicine, which includes population subgroups as well as individuals, thus avoiding the possible misinterpretation of the term “personalised”. The concept, which was originally based on genetics, has also evolved to include other factors. Medical records increasingly contain PGx data along with so-called Medically Actionable Predisposition conditions.[23] Finally, there is a trend toward preventive medicine where PGx focuses on characterising populations in anticipation of possible treatments.[48] This is a global trend,[49] and a good example is provided by the GENOTRIAL project at the Hospital

de la Princesa (Madrid, Spain). This approach is part of a broader global strategy to collect all the biomarkers that show variation.[50] This new approach has been welcomed with great interest by the pharmaceutical industry for population selection in clinical studies.

Conclusions

The application of PGx data in routine clinical practice in Spain is similar to that in other countries, and has been advancing in parallel with precision medicine. Key elements for its development are translational research, governmental support, and specialist training.

Funding

None declared.

Author contributions

The authors declare that they have contributed equally to the concept, design, definition of intellectual content, literature search, data collection and analysis, and the preparation, editing, and review of this manuscript.

Liability and assignment of rights

All authors have fulfilled their responsibilities as defined by the International Committee of Medical Journal Editors (available at http://www.icmje.org/).

In the event of publication, all authors exclusively cede the rights of reproduction, distribution, translation, and public communication (by any means or sound, audiovisual, or electronic support) of this article to *Farmacia Hospitalaria* and by extension to the SEFH. To this end, a letter of ceding of rights will be signed at the time of sending the article through the online manuscript management system.

Declaration of competing interest

None declared.

References

1. Shi MM, Bleavins MR, de la Iglesia FA. Pharmacogenetic application in drug development and clinical trials. Drug Metab Dispos. 2001;29(4) 591-5.
2. Ministerio de Ciencia e Innovación. Estrategia española MPP 2020 (Página Web). (Citado 17-7-2023). Available from: https://www.ciencia.gob.es/Noticias/2020/importadasVINETTE/septiembre/El-Gobierno-lanza-la-Estrategia-Espanola-de-Medicina-Personalizada-con-mas-de-25-millones.html.
3. National Research Council Committee on A Framework for developing a new taxonomy of disease. Toward precision medicine: Building a knowledge network for biomedical research and a new taxonomy of disease. Natl Acad Press; 2011 doi: 10.17226/13284.
4. Hicks JK, Aquilante CL, Dunnenberger HM, Gammal RS, Funk R, Aitken SL, et al. Precision pharmacotherapy: integrating pharmacogenomics into clinical pharmacy practice. JACCP. 2019;2(3):303–13. doi: 10.1002/jac5.1118.
5. Bishop JR, Ellingrod VL. Precision pharmacotherapy enables precision medicine. Pharmacotherapy. 2017;9:985-7. doi: 10.1002/phar.1998.
6. OECD. Tackling Wasteful Spending on Health (Monografía en Internet). Paris: OECD Publishing; 2017. (Citado 17-7-2023). Available from: https://read.oecd-ilibrary.org/social-issues-migration-health/tackling-wasteful-spending-on-health_9789264266414-en#page4.
7. Nunez-Torres R, Pita G, Peña-Chilet M, López-López D, Zamora J, Roldán G, et al. Comprehensive analysis of 21 actionable pharmacogenes in the Spanish population: from genetic characterisation to clinical impact. Pharmaceutics. 2023;15:1286. doi: 10.3390/pharmaceutics15041286.
8. Clinical Pharmacogenetics Implementation Consortium (CPIC). Pharmacogenomics Knowledge Base (base de datos en Internet). Stanford University. (Citado 17-7-2023). Available from: https://www.pharmgkb.org/
9. Pharmacogene Variation (PharmVar) Consortium (Página Web). (Citado 17-7-2023). Available from: https://www.pharmvar.org/.
10. National Library of Medicine. ClinVar (Base de datos en Internet). Bethesda, MD: US National Institutes of Health. (Citado 17/07/23). Available from: https://www.ncbi.nlm.nih.gov/clinvar/
11. US Food and Drug Administration. Table of Pharmacogenetic Associations (Base de datos en Internet). (Citado 17/07/2023). Available from: https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations.
12. US Food and Drug Administration. Table of pharmacogenomic Biomarkers in Drug Labeling (Base de datos en Internet). (Citado 17-7-2023). Available from: https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling.
13. European Medicines Agency (EMA). European Union. (Página Web). (Citado 17/07/2023). Available from: https://www.ema.europa.eu/en/search/search?search_api_views_fulltext=genomic%20biomarkers.
14. SwissMedic, Swiss Agency for Therapeutic Product. Swiss Government. (Página Web). (Citado 17/07/2023). Available from: https://www.swissmedic.ch/swissmedic/en/home/about-us/swissmedic–swiss-agency-for-therapeutic-products.html.
15. Pharmaceuticals and Medical Devices Agency, Japan (PMDA). Government of Japan. (Página Web). (Citado 17/07/2023). Available from: https://www.pmda.go.jp/english/.
16. Health Canada (Santé Canada) (HCSC). Government of Canada (Página Web). (Citado 17/07/2023). Available from: https://www.hc-sc.gc.ca/.
17. Clinical Pharmacogenetics Implementation Consortium (CPIC). Genes-Drugs (Base de datos en Internet); Stanford University & St. Jude Children's Research Hospital (Citado 17/07/23). Available from: https://cpicpgx.org/genes-drugs/
18. Swen JJ, Nijenhuis M, van Rhenen M, de Boer-Veger NJ, Buunk AM, Houwink EJF, et al. Pharmacogenetic information in clinical guidelines: the European perspective. Clin Pharmacol Therap. 2018;103(5):795–801. doi: 10.1002/cpt.1049.
19. Lunenburg CATC, van der Wouden C, Nijenhuis M, van Rhenen MHC, de Boer-Veger NJ, Buunk AM, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene–drug interaction of *DPYD* and fluoropyrimidines. Eur J Hum Genet. 2020;28:508–17. doi: 10.1038/s41431-019-0540-0.
20. Nijenhuis M, Soree B, Jama WOM, de Boer Verger NJ, Buunk AM, Guchelaar HJ, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction of *CYP2D6* and *COMT* with atomoxetine and methylphenidate. Eur J Hum Genet. 2022 Dec 12. doi: 10.1038/s41431-022-01262-z.
21. Brouwer JMJL, Nijenhuis M, Soree B, Guchelaar HJ, Swen JJ, van Schaik RHN, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2C19 and CYP2D6 and SSRIs. Eur J Hum Genet. 2022;30(10):1114–20. doi: 10.1038/s41431-021-01004-7.
22. Beunk L, Nijenhuis M, Soree B, de Boer-Veger NJ, Buunk AM, Houwink EJF, et al. Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2D6, CYP3A4 and CYP1A2 and antipsychotics. Eur J Hum Genet. 2023. doi: 10.1038/s41431-023-01347-3.
23. NIH National Library of Medicine National Center for Biotechnology Information. dbSNP (Base de datos en Internet). Bethesda, MD: US National Institutes of Health; (Citado 17/07/2023). Available from: https://www.ncbi.nlm.nih.gov/snp/
24. Van der Lee M, Kriek M, Guchelaar HJ, Swen JJ. Technologies for pharmacogenomics: a review. Genes. 2020;4;11(12):1456. doi: 10.3390/genes11121456.
25. Sociedad Española de Farmacia Hospitalaria. Mapa de Unidades de Farmacocinética/Farmacogenética (Base de datos en Internet). (Citado 17-7-2023). Available from: https://www.google.com/maps/d/viewer?mid=1pG7c13mK6sBjewCYPDGAd7djJ-Eblc2x&ll=37.138827266630884%2C-7.656440792544002&z=8.
26. Volpi S, Bult CJ, Chisholm RL, Deverka PA, Ginsburg GS, Jacob HJ, et al. Research directions in the clinical implementation of pharmacogenomics: an overview of US programs and projects. Clin Pharmacol Ther. 2018;103(5):778–86. doi: 10.1002/cpt.1048.
27. Liu M, Vnencak-Jones CL, Roland BP, Gatto CL, Mathe JL, Just SL, et al. A tutorial for pharmacogenomics implementation through end-to-end clinical decision support based on ten years of experience from PREDICT. Clin Pharmacol Ther. 2018;103(5):778–86. doi: 10.1002/cpt.1048.
28. Alshabeeb MA, Deneer VHM, Khan A, Asselbergs FW. Use of pharmacogenetic drugs by the dutch population. Genet. 2019:10 doi: 10.3389/fgene.2019.00567.
29. Borobia AM, Ia Dapi, Tong HY, Arias P, Muñoz M, Tenorio J, 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. 2018;11:189–99. doi: 10.1111/cts.12526.
30. Estrategia general de implementación clínica de la farmacogenética de la SEFF (Monografía en Internet). Sociedad Española de Farmacogenéntica y Farmacogenómic. 2023 (Citado 17-7-2023). Available from: https://seff.es/wp-content/uploads/2023/01/ESTRATEGIA-DE-IMPLAMENTACION-DE-LA-SEFF.pdf.
31. Zubiaur P, Mejía-Abril GI, Navares-Gómez M, Villapalos-García G, Soria-Chacartegui P, Saiz-Rodríguez M, et al. PriME-PGx: La Princesa university hospital multidisciplinary initiative for the implementation of phamacogenetics. J Clin Med. 2021;10:3772. doi: 10.3390/jcm10173772.
32. LLerena A, Peñas-LLedó E, de Andrés F, Mata-Martín C, Sánchez CL, Pijierro A, et al. Clinical implementation of pharmacogenetics and personalized drug prescription based on e-health: the MedeA initiative. Drug Metab Pers Ther. 2020;1;35(3). doi: 10.1515/dmpt-2020-0143.

33. Medicina personalizada de precisión en España. Mapa de comunidades. (Monografía en Internet). Fundación Instituto Roche; 2019. (Citado 17-7-2023). Available from: https://www.institutoroche.es/recursos/publicaciones/181/medicina_personalizada_de_precision_en_espana_mapa_de_comunidades.
34. Peña-Chilet M, Roldán G, Perez-Florido J, Ortuño FM, Carmona R, Aquino V, et al. CSVS, a crowdsourcing database of the Spanish population genetic variability. Nucleic Acids Res. 2021;49:D1130–7. doi: 10.1093/nar/gkaa794.
35. Momozawa Y, Mizukami K. Unique roles of rare variants in the genetics of complex diseases in humans. J Hum Genet. 2021;66:11–23. doi: 10.1038/s10038-020-00845-2.
36. Sasaki S, Mello CC, Shimada A, Nakatani Y, Hashimoto S, Ogawa M, et al. Chromatin-associated periodicity in genetic variation downstream of transcriptional start sites. Science. 2009;323(5912):401–4. doi: 10.1126/science.1163183.
37. Cavallari LH, Lee CR, Duarte JD, Nutescu EA, Weitzel KW, Stouffer GA, et al. Implementation of inpatient models of pharmacogenetics programs. Am J Health System Pharm. 2016;73(23):1944–54. doi: 10.2146/ajhp150946.
38. Caudle KE, Hoffman JM, Gammal RS. Pharmacogenomics implementation: "a little less conversation, a little more action, please". Pharmacogenomics. 2023;24:4. doi: 10.2217/pgs-2023-0020.
39. Analysis of barriers, guidelines and best practices for implementation of results and data exploitation in personalised medicine research projects (Monografía en Internet). Eur Partner Personal Med. 2023. (Citado 17-7-2023). Available from: https://www.icpermed.eu/media/content/Overcome_Barriers_in_Personalised_Medicine_Research.pdf.
40. Roncato R, Dal Cin L, Mezzalira S, Comello F, De Mattia E, Bignucolo A, et al. FARMAPRICE: a pharmacogenetic clinical decision support system for precise and cost-effective therapy. Genes. 2019;4;10(4):276. doi: 10.3390/genes10040276.
41. NIH National Library of Medicine. Genetic Testing Registry (Base de datos en Internet). Bethesda, MD: US National Institutes of Health; (Citado 17-7-2023). Available from: https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=125853
42. Infraestructura de Medicina de Precisión asociada a la ciencia y a la tecnología. IMPaCT. Plan Estratégico. (Monografía en Internet). Instituto de salud Carlos III; 2023. (Citado el 17-7-2023). Available from: https://www.isciii.es/QueHacemos/Financiacion/Documents/IMPaCT%20Web/PLAN_ESTRATEGICO_IMPaCT.pdf.
43. Bernstein JA. Precision medicine/personalized medicine: a critical analysis of movements in the transformation of biomedicine in the early 21st century. Cad Saúde Pública. 2019;35(3), e00153118. doi: 10.1590/0102-311X00153118.
44. Universidad de Granada. Cooperation in Quality Assurance in Pharmacy Education and training between Europe and Latin America (COPHELA). (Página Web). (Citado 17-7-2023). Available from: https://www.cophela.eu/es/cophela-programme.
45. Haidar CE, Petry N, Oxencis C, Douglas JS, Hoffman JM. ASHP statement on the pharmacist's role in clinical pharmacogenomics. Am J Health-Sys Pharm. 2022;79(8):704–7. doi: 10.1093/ajhp/zxab339.
46. Roederer MW, Kuo GM, Kisor DF, Frye RF, Hoffman JM, Jenkins J, et al. Pharmacogenomics competencies in pharmacy practice: A blueprint for change. J Am Pharm Assoc. 2017;1:120–5. doi: 10.1016/j.japh.2016.08.014.
47. Christensen KD, Bell M, Zawatsky C, Galbraith LN, Green RC, Hutchinson AM, et al. Precision population medicine in primary care: the Sanford Chip experience. Front Genet. 2021;12:1–10. doi: 10.3389/fgene.2021.626845.
48. Elewa H, Awaisu A. Pharmacogenomics in pharmacy practice: current perspectives. Integr Pharm Res Pract. 2019;8:97–104. doi: 10.2147/IPRP.S180154.
49. Haidar CE, Crews KR, Hoffman JM, Relling MV, Caudle KE. Advancing pharmacogenomics from single-gene to preemptive testing. Annu Rev. Genom Hum Genet. 2022;23(1):449–73. doi: 10.1146/annurev-genom-111621-102737.
50. The International Genome Sample: IGSR (Base de datos en Internet). EMBL's European Bioinformatics Institute (Citado 17-7-2023) Available from: 1000 Genomes | A Deep Catalog of Human Genetic Variation (internationalgenome.org).