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Challenges of Clinical Pharmacogenomics Implementation in the Era of Precision Medicine

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ABSTRACT

While pharmacogenomics (PGx) presented to many as the poster child of personalized medicine, in the context of moving away from the "one size fits all" model of pharmacological therapy of diseases to a more tailored approach addressing the individuality of each person, the application of PGx has been hindered by numerous challenges. These challenges range from issues with study designs in scientific research, both clinical and for discovery, policy and regulatory hurdles affecting insurance coverage, to the very fundamental need for adequate training for laboratorians, physicians, and pharmacists. Moreover, access to services and addressing health disparities in personalized medicine generally and PGx specifically remain a complicated endeavor. PGx-related ethical, legal, and social issues continue to be a point of concern for those looking to implement PGx in clinical practice. Additionally on the technical side, the speed with which next generation sequencing (NGS) technologies have evolved, generating tens of thousands of rare PGx variants adds a new layer of challenges requiring accurate interpretation and assessment of functional role of novel variants to determine their impacts on drug response and possible toxicities. Without consensus and standardized approaches to testing and interpretation, integration of PGx into routine clinical care becomes an unattainable task. In this article we aim to address some of the challenges that impede broad adoption of clinical PGx testing, and to shed the light on needed steps towards a successful implementation of PGx, with the goal of improving health outcomes individually and for the general population.

Introduction

Precision medicine, which is often interchangeably used with personalized or individualized medicine, is defined as an innovative approach to prevention, diagnosis and treatment of individuals, taking into account the individual's genomic, environmental and lifestyle profile to guide decisions related to their medical management[1,2]. Pharmacogenomics (PGx), the science that studies the intersection between one's genetic make-up and response to pharmacological therapies, plays a pivotal role in precision medicine driving biomarker discovery, guiding the development of targeted therapeutics, improving treatment outcomes, and preventing adverse effects[3,4]. Yet, in clinical practice, precision medicine initiatives including PGx, have met major hurdles when it comes to application. The lack of strategic clarity with regards to basic research in PGx is one of the important challenges that needs to be addressed. While hundreds of genes influencing drug response have been identified, investigating the genetic variability of such genes and their functional and clinical effects lags behind, particularly for novel or rare variants, and among populations less genetically characterized[5-7], and requires in parallel efforts of large-scale and high-throughput functional studies and improvement of in-silico prediction tools. Additional challenges include, but not limited to, the complexity of studying non-genetic contributors to drug response phenotypes, limited research of epigenetic elements, and the need for integration of multifactorial genetic models. Regarding clinical and translational PGx research, addressing lack-of-evidence concerns of regulatory agencies and physicians by proving the clinical utility of PGx testing, remains a top research goal. While the expansion of use of PGx in drug development clinical trials by pharmaceutical companies is a positive trend[8], these clinical studies remain challenged by the small sample size, lack of genetic diversity, and concerns over patients' privacy and related ethical considerations[9].

Over the last couple of decades, the genomic technologies have exploded in terms of its throughput, size of data generated, and in the speed of novel variant discovery and in the type of variants revealed. While this progress is to be celebrated, it represents a challenge particularly for the field of PGx. Clinical laboratories struggle with the lack of standardization practice guidelines and continue to strive to identify the ideal method of integrating laboratory reports to the electronic health records that hopefully would ease the clinical implementation[10]. Computational modeling, artificial intelligence (AI), and Machine Learning (ML) applications in PGx carry a lot of promise yet the integration of such tools remains limited[11-13]. When it gets to the implementation in the clinic, PGx faces multiple levels of complexities that need to be overcome for a seamless utilization of PGx information in patient care. This starts with the need for training laboratorians and clinicians and extending into choosing the appropriate technology and identifying the proper methods for generating, bioinformatically-processing and storing the large amount of data the current next generation sequencing (NGS) technologies generate[5,14-16]. Responding to the needs of the PGx community, there has been multiple efforts for standardizing selection, nomenclature, functional determination of alleles, as well as for establishing genotype-based prescribing guidelines for established drug-gene pairs[17-21]. Resistance to the implementation of PGx, goes back often to the unresolved question of cost effectiveness despite evidence favoring the economic outcome of PGx implementation[22-24]. Similarly, whether PGx should be performed preemptively, at point of care or even whether there is room for direct-to-consumer PGx testing, remain unanswered[25-29]. Additionally, the issue of health disparities looms large on the efforts to implement precision medicine and PGx whether in research, clinical trials design, or final implementation, and ought to be addressed[30-32], not simply as the moral thing to do, but it is equally a long-term investment in individual and community health[33,34]. Lastly, there are social, legal and ethical consideration relating to PGx research and implementation [9,35,36]. In this article, we will give an overview of the challenges facing clinical PGx implementation. We will discuss challenges relating to PGx research and discovery including translational research. We will also address

the hurdles faced while utilizing newer technologies and those met when trying to implement PGx into the clinic. Lastly, we will discuss social, legal and ethical issues to be considered for a successful implementation of PGx programs. Some of these challenges have been discussed by others but we will attempt to give a comprehensive overview of most of these issues. Understanding and debating such challenges open doors for identifying solutions with the goal of realizing the potential that PGx and precision medicine can have for improving health outcomes of our patients.

PGx Research and Discovery

GENETIC VARIATIONS AND FUNCTIONAL CONSEQUENCES

Genes involved in pharmacodynamics and pharmacokinetics pathways and in clinical drug response phenotypes are referred to as pharmacogenes and can be classified functionally into drug transporters (e.g. *SLCO1B1* and *ABCB1*), drug metabolizing enzymes (e.g. *CYP2D6* and *TPMT*), drug targets (e.g. *CFTR*), and major histocompatibility complex genes (e.g. *HLA-B*:*15:02)[37]. Variations in these genes are quite common in the population[38-40]. While most basic and translational PGx research has focused on these common variations, a significant fraction of heritable variability of these genes remains unknown and is thought to be explained, at least in part, by rare genetic variations that might be unique to specific populations and call for population-adjusted genetic profiling[5,41-45]. With the cost of genomic techniques going down, and the public availability of large population-wide sequencing data, more efforts are warranted to be directed at exploring such rare variants in pharmacogenes, specially that early studies suggest that there is an abundance of rare variants in genes involved in drug response[44,46]. The challenge is in deciphering the functional significance of these rare variants given the cost, the laborious nature of systems biology modeling approaches, the complexity of *in vitro* assays such as heterologous variant expression in cell lines which does not always reflect the *in vivo* effects, and the infeasibility of performing epidemiological association studies to determine the variants' impact on patients given the huge number of variants to be interrogated[47]. For these reasons, computational predictions have been utilized as an alternative to investigate the functional consequences of newly identified variants. In-silico tools such as SIFT[48] or PolyPhen-2[49] depend on sequencing conservation, structure stabilities, and functional genomic data to predict variants' function. Additionally, researchers generally consider that variants that result in stop codons, frameshifts or splice defects to be potentially damaging[5,47]. Yet these prediction tools, were designed to be used within the context of disease-associated or disease-causing mutations and studies have shown they underperform when handling PGx datasets due to the differences in design related to the required training sets, and the fact that using evolutionary conservation for variant effect prediction in the context of disease, cannot be applied in PGx where many genetic variants are not conserved, or whole genes could be totally deleted, e.g. *CYP2D6*[47,50]. Fortunately, more work is being performed towards developing PGx variants prediction tools that are showing promising results[47,51], including some tools that are gene-specific predictors such as tools designed to investigate *DPYD*[52] and *CYP2D6*[53].

NEW AREAS OF PGx RESEARCH: GENETIC AND NON-GENETIC

A new area of genetic research where PGx seems to fit, is the research into polygenic risk scores (PRS), given the established understanding that patients' drug response phenotype relies on multiple factors, whether it is drug properties or PK or PD factors and the proven limitation of individual genetic marker association models[54]. Yet while in theory, PGx seems to be an ideal area for application of PRSs, many barriers still exist such as the need to demonstrate clinical utility, the need for large patient cohorts including replication cohorts, and the needed education and collaboration between various stakeholders prior to the implementation[55-57]. While part of the missing heritability in variation in drug

response could be attributed to rare variants as discussed earlier[58], another part could be explained by epigenetic phenomena such as DNA methylation, and histone acetylation in a new growing field of research called pharmaco-epigenomics, a dynamic process that can affect drug response in a time-, environment-, and tissue-dependent manner[59,60]. The field of pharmaco-epigenomics is still new, and much research is needed to understand instances when the epigenetic state affects drug response, and when drugs can affect an individual's epigenetic profile by altering gene expression for example[61].

While most basic PGx research had focused on the genetics factors affecting drug response, non-genetic and environmental factors need to be addressed systematically. Age, sex, ethnicity, lifestyle, co-administered medications, etc., are among factors that are known to influence one's response to medications and should be considered for a more comprehensive understanding within a framework that includes investigation of gene-gene and gene-environment interactions with regards to the genetic architecture of response to commonly prescribed drugs[62-64]. Additionally, more consideration should be given to the way studies are designed for better definition of the clinical phenotypes that includes analysis of potential confounding factors and incorporating metabolomic or proteomic data[65,66].

Translational PGx Research

CLINICAL UTILITY STUDIES

Despite major advancements and discoveries in the field of PGx in the last few decades, translation into routine clinical practice remains lagging and many clinical practice guidelines like those published by the American College of Gastroenterology (ACG) or National Comprehensive Cancer Network (NCCN), to name a few, have limited or inconsistent inclusion of PGx testing recommendations[67]. This could be attributed to the disconnect between clinical validity versus clinical utility studies. While clinical validity for multiple gene-drug pairs have long been established particularly in the context of published guidelines[19,68], studies on PGx clinical utility are lacking and limited by the small sample size and lack of statistical power, which providers, policy makers and payers always reference as a requirement to prove value prior to implementation[69-71], in addition to the unresolved debate on what level of evidence is required to support clinical implementation[71,72]. This was the impetus for efforts to establish a standardized approach to evaluating the evidence of clinical utility for PGx testing by the Standardizing Laboratory Practices in Pharmacogenomics Initiative (STRIPE)[73]. STRIPE investigators created a task force aiming at recommending study designs to demonstrate clinical utility as required by various stakeholders. Such standardization efforts regarding power, consideration of confounding factors, and test statistics are fundamental for clinical PGx studies to demonstrate acceptable clinical utility[7]. It is also of paramount importance to establish a standardized approach to defining drug response phenotypes particularly in clinical trials, including defining acceptable surrogate end points. While the use of surrogate end points can accelerate clinical trials, there are currently no clearly defined guidance for acceptability of such surrogates[74,75]. Accordingly, the need for well-designed, replicable large studies, which might only be possible through multi-institutional or even multi-national collaborations, becomes a must[76,77]. An alternative would be utilization of large-scale population studies such as the UK-Biobank or the All-of-Us program in the USA which have opted to return PGx results to the participants[78,79]. Analyzing data from such large studies does require bioinformatic tools and algorithms specific for PGx data[80-83], in addition to the need for strategies to resolve discrepancies that might arise related to the nomenclature and functional interpretation[84,85]. It is worth noting that multiple studies have investigated if PGx testing influenced and/or improved clinical decisions and outcomes, with promising results demonstrating up to 30% decrease in serious side events as PGx testing enabled actionable medication recommendations[86,87], in addition to improving clinical outcomes including quality of life[88,89], and decreasing hospitalizations and emergency department visits[90,91].

COST EFFECTIVENESS OF PGx TESTING

Adoption and implementation of PGx by health systems is also hindered frequently by low or absent reimbursement as payers' demand evidence of downstream cost savings to justify coverage[92], even though adverse drug reactions, which could be avoided by pre-emptive PGx testing, are a major cause of morbidity and mortality with a huge estimated annual cost of up to billions of dollars[93-95]. Multiple systematic evidence review articles that looked at studies that evaluate the economic value of PGx testing, have identified definitive evidence of the cost-effectiveness or cost-saving of PGx testing particularly for drug–gene pairs with FDA labeling or Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines[22,24,96,97]. For example, 44% and 96% of the studies found that PGx testing for warfarin and clopidogrel respectively, showed evidence of cost effectiveness and/or savings[22]. Another analysis looked at cost effectiveness of PGx testing in preventing deaths related to adverse drug reactions, and found savings over 51,000 euros (or $56,000) per prevented death with gained quality-adjusted life years (QALY), and even claimed this to be an underestimate[97]. An economic simulation analysis of possible savings when using antihypertensives from payers perspective used a multi-gene panel to guide medication based on genetic background and demonstrated possible savings over 50% of the cost of managing hypertensive patients estimated at over $40 billion over a 3-year period[98]. These examples demonstrate the cost-effectiveness of clinical PGx testing whether from public[99] or from private payers' [97] perspectives, for single gene[100] or multigene panels[98,101], and for individual disorders or when applied across the board in health systems or insurance coverage programs[102-104].

PGx and New Technologies

The advent of new genotyping technologies such as NGS has offered unprecedented opportunities for giving a more comprehensive picture of the genetic makeup of patients. Such technologies and advances came with their own set of challenges that did not spare the field of PGx[58,105]. NGS offers a fast, relatively inexpensive, high-throughput DNA sequencing approach that can come in different formats, from single gene to multi-gene panels, to whole exome sequencing (WES), and currently whole genome sequencing (WGS) approach. At the same time, NGS expands the scope of genomic variant and variant types that that can be interrogated whether that be rare or common variants, single nucleotide polymorphisms (SNPs), copy number variations or structural variations, coding or non-coding alleles[106]. The technology is also continuously and rapidly evolving in terms of accuracy and versatility. While majority of applications still rely on short-read sequencing, a lot of progress has been achieved with the use of long-read sequencing technologies[107]. For NGS applications that target coding sequences, detecting variants in pharmacogenes that reside in such sequences, is technically feasible and in most cases non-problematic. Challenges arise though when the variants targeted are within non-coding sequences or within regulatory and untranslated regions, or when the pharmacogenes of interest are inherently difficult to sequence such as Cytochrome P450 2D6 gene (*CYP2D6*)[108] or loci within the human leukocyte antigen (HLA) genes[109]. Additionally, for genes where copy number or structural variants detection is of value (e.g. *CYP2D6*), and generally where haplotypes are to be called and phased, extra bioinformatic steps or tools are needed to be added to pipelines that are routinely used to detect single nucleotide or small insertion or deletions variants. Tools such as Stargazer[110] or Cyrius[111] have been designed to specifically call *CYP2D6* alleles. While tools such as Aldy[112] Pgxtools and StellarPGx[113,114] can analyze any sequenced pharmacogenes. A challenge remains though in the variable performance of such tools, differences in sensitivity and need for training datasets and continuous updates as PGx databases grow and change[115]. Long-read sequencing carries the promise of resolving many of the limitations of short-read sequencing in terms of sequencing complex regions of the genome and enabling phasing[116,117], but with the high cost, the long turn-around-time and the need for more sophisticated bioinformatic tools for analysis, the clinical utility of

long-read sequencing currently remains limited[118]. The large amount of data generated by NGS, particularly within the context of large databases or biobanks, requires special attention to management of "big data" whether that is data collection and processing, data storage, and results interpretation for clinical implementation, including search, sharing, transfer, visualization, querying, privacy and monitoring updates[81,119]. The need for specialized tools to address such needs, opened the door for applications of AI or more specifically its subfield of ML in PGx. ML is defined as the study of computer algorithms that improve automatically through experience, and in application are methods that allow obtaining satisfactory results in term of prediction and classification[12,120]. Studies that have investigated the use of ML in precision medicine and PGx had shown promising results particularly in psychiatry and cancer[121-124]. It is worth noting that the performance of ML techniques is currently limited by the need for large complex datasets for better performance, the lack of standardized procedures, and the difficulty of interpreting data[12,125].

Challenges Related to Clinical PGx Implementation

THE NEEDS FOR STANDARDIZATIONS

Practical implementation of PGx testing into the clinic has yet another set of roadblocks to be added to those previously discussed in this review such as basic science or clinical research challenges, as well as those related to the current technologies. In an attempt to address the problem of lack of standardization of PGx practices across the world, it has been proposed that the creation of an international body of experts to guide universal research and implementation efforts allowing for larger access to data and exchange of expertise could help harmonize PGx implementation efforts[126]. Such approach of uniting behind a single body or entity, seems too optimistic to apply. Different countries and regions of the world, have their own specialized entities and regulations that might not be easily harmonized into a global effort.

Consideration should also be given to the fact that underserved communities and underdeveloped countries lag in terms of knowledge, access to resources and the economic challenges implementing PGx might impose on their already strained health systems[127,128]. Additionally, it is important to define population-specific PGx marker frequencies and to formulate country-specific recommendations for drug efficacy and safety[129-131]. Even within individual countries, PGx implementation efforts differ significantly in scope, cost, available tests, workforce education and diversity of populations served[132].

Lack of standardization is not only limited to general PGx practices but extends to lack of standardization of nomenclature of PGx variants. For example, star (*) allele nomenclature is used in PGx to describe allelic variations or haplotypes within pharmacogenes. The base of using star alleles was the genetic linkage between pharmacogenes variants and the need to have a standardized way of communicating such variations and their predicted function to help in translation into clinical action[133]. Despite that, there remains extensive variability of PGx terminology used in research and clinical contexts[134]. This is becoming the more complicated with the explosion of genetic data in the era of NGS that require careful curation and annotation[133,135]. To address that need, The Pharmacogene Variation Consortium (PharmVar) was built as a central repository for pharmacogene (PGx) variations that focuses on haplotype structure and allelic variation[21]. The standardized variation within Pharmvar is then used by the Pharmacogenomics Knowledgebase (PharmGKB) and the Clinical Pharmacogenetic Implementation Consortium (CPIC), and the three entities work closely within the Pharmacogenomics Research Network (PGRN; https://www.pgrn.org)[20], and with other PGx-related professional organizations or communities. Most recently, the ClinPGx initiative aims to consolidate and centralize these various resources[136]. While such efforts of standardization are commendable, until everyone adopts the same nomenclature, communication in the field of PGx and ability to combine datasets between various research and clinical groups will remain limited.

Additionally, standardizing the guidelines that clinicians need for accurate prescribing of the right drug at the right dose remains none-ideal. Regulatory bodies and various research consortia in different parts of the world, work on publishing guidance for well-established gene-drug associations that can be used in clinical practice. Examples of such entities are the U.S. Food and Drug Administration (FDA) and its counterparts such as the European Medicine Agency (EMA), and the Japanese pharmaceutical and medical device agency. CPIC and the Dutch Pharmacogenetics Working Group (DPWG) are examples of the research consortia that publish guidelines based on the existing scientific evidence. The question then becomes, how can recommendations and guidelines from the U.S., Europe or other developed countries be applied outside these regions given the differences in allele frequencies and genetic backgrounds in different parts of the world? Particularly, when guidance from these entities already shows significant heterogeneity even for the same gene-drug pairs and even when the same evidence is used[137]. As a result, until an international effort is in place to develop basic guidance that can be universally adopted, and until there is better understandings of heterogeneity in available guidance, the utility of such guidelines and ability to generalize their use to determine the proper drug and dose for each patient remains elusive. Moreover, given the variability in PGx testing technologies used by various clinical laboratories, in addition to the variability in genes and alleles being tested in one laboratory versus the other, there is a practical need for standardizing important genes to be tested and at least a minimum number of alleles that need to be present for a test to be of meaningful utility. To address that clinical practice gap, the Association for Molecular Pathology (AMP) Clinical Practice Committee's Pharmacogenomics (PGx) Working Group published a series of documents to define the key attributes of PGx alleles recommended for clinical testing, and to determine a minimal set of variants that should be included in clinical PGx genotyping assays. So far, they have published genotyping recommendations for multiple important genes such as *CYP2D6, CYP3A4 and 5* and *NUDT15* to name a few, and classified variants into tier 1 (must test alleles) and tier 2 (optional alleles)[138-140]. Adoption of such genotyping allele recommendations could help streamline data sharing between clinicians and facilitate PGx implementation.

MODELS OF PGx TESTING

Currently, there are multiple models of PGx testing whether pre-emptively, as a routine clinical test or at-point-of-care. Pre-emptive PGx testing has proven to be both feasible and beneficial[141,142], yet payers still have concerns and show preference for outcomes from randomized controlled trials, and insist on additional studies to demonstrate an impact on clinical decision making[143]. Moreover, preemptive PGx testing requires an established infrastructure for laboratory testing, interpretation and incorporation of results into electronic medical records (EMRs) which might not be available for community-based and primary care practice environments[144]. Routine PGx testing on the other hand can have a turn-around time of several days which is not ideal in an urgent care setting where drugs like clopidogrel or warfarin need to be properly dosed in a timely fashion[145]. This is where the model of point-of-care testing comes into play; such model would allow for a rapid turn-around time for PGx testing that would be available for providers at the time of prescribing the medications. The model has its own limitations though, in terms of the novelty of such approach, and lack of experience implementing the model in clinical settings. To be able to implement point-of-care PGx testing as a routine practice, several issues need to be considered such as provider preparation, laboratory certification and technical capability, data management, and availability of clinical decision support and dosing algorithms[28,146]. Several studies including randomized controlled trials for point-of-care genotype-guided dosing of warfarin for example, showed that approach to be superior to standard dosing with respect to both the primary outcome measure (time in the therapeutic INR range) and a number of secondary outcome

measures, yet it remains debatable whether these findings translate into cost-effectiveness and clinically significant outcomes[147,148].

CLINICAL DECISION SUPPORT

To facilitate the clinical adoption of PGx, it was established that providers need electronic clinical decision support (CDS) systems to be in place[149,150]. CDS systems are excellent tools to address knowledge gaps in PGx that are often cited by physicians as a challenge for PGx implementation[151]. Many studies have proven the feasibility of implementing a PGx decision support solution, either in a multinational, multi-center setting[152], or in individual institutes[153]. It is important to note that implanting such systems is complex and there are hurdles to building and using such tools and these systems are costly to build and maintain[154,155]. Moreover, providers who would use these CDS systems need to be engaged and well-trained. CDS also needs to be easily integrated into EHRs, be continuously updated, be user-friendly, compliant with regulations and be customizable[156,157].

PROVIDERS EDUCATION

When investigating health care providers' attitudes towards PGx implementation, it is astounding to see the major disconnect between the enthusiasm and the sense of unpreparedness to use PGx to guide patient care[158]. Most studies find positive attitudes towards the potential use of PGx testing and its promise of improving outcomes and minimizing adverse reactions, yet many share their concerns over lack of familiarity with PGx testing affecting their ability to interpret and communicate test results, in addition to concerns about insurance coverage and reimbursement given the lack of demonstrated clinical utility studies[158]. In addition to working towards more inclusion of PGx education in medical curricula and training[159], establishing more synergy between physicians of different specialties and clinical geneticists and pharmacists familiar with ordering and interpreting PGx results might help bridge such PGx knowledge gap[151,160].

INSURANCE COVERAGE AND REIMBURSEMENT

Despite the field of PGx taking strides in the last few decades, with research showing feasibility, cost-effectiveness while improving clinical outcomes[161,162], insurance coverage and reimbursement are still lagging, although improving[163-165]. In their study published in 2019, Park et.al., investigated PGx coverage by various health insurance companies, and concluded that the coverage and payments of the tests varied by company and by gene-drug pairs and remain suboptimal[164]. Similarly, when looking at PGx coverage in case of cancer, it was observed that there were substantial variations with regards to single genes versus multigene panels among different payers with discrepancies among coverage policies and clinical guidelines[163]. Despite that, there has been some improvement in the last few years. The largest U.S. private payer, United Health Group, approved the use of PGx for antipsychotics and antidepressants in 2019, followed by Medicare expanding its PGx coverage in 2020[166]. In 2021, U.S. Centers for Medicare & Medicaid Services (CMS), issued the Local Coverage Determination (LCD), L39063, for PGx testing, requiring that the patient tested has a clinical condition that a PGx test result would directly impact the drug management of this patient's condition; and that the test meets evidence standards and clinical utility defined by some of the authoritative entities such as CPIC or FDA in these domains[167]. To guarantee patient access to personalized medicine, including PGx, joint efforts by various stakeholders including patients, healthcare providers, industry, government agencies, payers, and health policy organizations need to focus on advocating for PGx as an efficient and timely value-based decision-making tool, aligning reimbursement with available evidence[168].

Ethical, legal and social challenges for PGx implementation

GENETIC DISCRIMINATION AND STIGMATIZATION

When addressing challenges for clinical PGx implementation, the focus is usually on research, clinical, technical, and logistical difficulties, while ethical, social and possible legal considerations are not as commonly discussed. Most of the latter challenges apply to any field where genetic testing

is used, in this case, to PGx particularly with the expansion of precision medicine initiatives resulting in large datasets of genetic testing results. There are growing ethical concerns related to the use of such data. One concern for example is fear for genetic discrimination which might occur when genetic information is adversely used to affect individuals' access to health care and related services or to compromise patients' autonomy, privacy, or confidentiality[169]. To address this concern, many federal regulations in the United States have been put in place to prevent such discrimination. These regulations are detailed in the statement of the American College of Medical Genetics and Genomics (ACMG) regarding genetic discrimination[170]. Similar efforts have been considered in other parts of the world[171,172]. A closely related concern if fear of stigmatization, when a person suffers differential treatment based on their assumed genetic characteristics[173,174]. In addition to their roles in preventing genetic discrimination, the Health Insurance Portability and Accountability Act (HIPAA) and the Genetic Information Nondiscrimination Act (GINA), play a pivotal role in ensuring patients privacy while balancing that with the rights of other individuals and the public to access the information, for example, to inform at-risk relatives or to be used for public health purposes[175,176].

CONSENT, DATA OWNERSHIP, AND INCIDENTAL FINDINGS

As is the case for other applications of genetic testing, consenting individuals for PGx is essential yet remains complicated. As discussed earlier, there is major need for large cohorts and multi-institutional or multi-national studies to address the gaps in PGx research, and this highlights the question of how should patients be consented to be included in such studies, or if there is need for consent if samples are de-identified, with the caveat that identity of individuals could be revealed when large genetic data is generated. There are no standards or guidelines for consenting patients for genetic testing in general and for PGx in particular and perhaps it is time to address such need to guarantee patient autonomy and privacy while continuing to advance science[9,177]. One other unresolved issue is the ownership of the biological material and genetic data resulting from genetic testing including PGx. Are individuals entitled to ownership of their genetic material if they consented to research? Or is it the right of research institutions where the research is conducted? What about the private sector and pharmaceutical companies if they are research partners?[178,179] So far there are no universal protocols or guidelines for such delicate matter and more and more legal concerns are being brought to light as genomic medicine becomes common practice[180,181].

With the widespread use of next generation sequencing, the potential of identifying incidental findings which are defined as unexpected discoveries that are not related to the reason for the test, while performing PGx testing increases[182,183]. Attitudes of physicians and patients with regards to disclosing incidental findings when performing PGx testing do not always align and hence the importance of developing a strategy that takes into account the ethical obligations of health care providers while respecting the desires of patients and potential consequences of revealing such findings particularly if the data belongs to a child[184-186].

HEALTH DISPARITIES

Considerations of health disparities is yet another major social issue related to clinical implementation of PGx testing. Precision medicine initiatives carry a lot of promise in addressing health disparities yet concerns about lack of inclusion of minorities and disadvantaged populations in the research and development of precision medicine initiatives including PGx persist[187-189]. With regards to PGx, research has shown that there remain major hurdles to implementation, due to lack of diversity in studied populations, in terms of genetic ancestry, gender, age, socioeconomic status or even access to services based on geographical location[187,190-193]. In previous work by the authors, the relationship between PGx implementation and various determinants of health in the context of health disparities were detailed. The

concern is that without addressing such disparities, future PGx or precision medicine initiatives would only widen an already existing gap disfavoring underrepresented and disadvantaged populations[187].

Conclusion

Clinical PGx testing is becoming an integral part of the practice of precision medicine. Both carry a major promise of improving patient care by optimizing drug treatments, minimizing adverse drug reactions, improving drug efficacy and eventually cutting costs. Despite major efforts towards enabling implementation into clinical practice, the field still faces major challenges for much of the developed and more so for the developing world. Together with scientific advancements and newer technologies, concerted efforts by various stakeholders such as medical, regulatory and social entities are needed for the potential of PGx and precision medicine to be realized.

Conflicts of Interest Statement:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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