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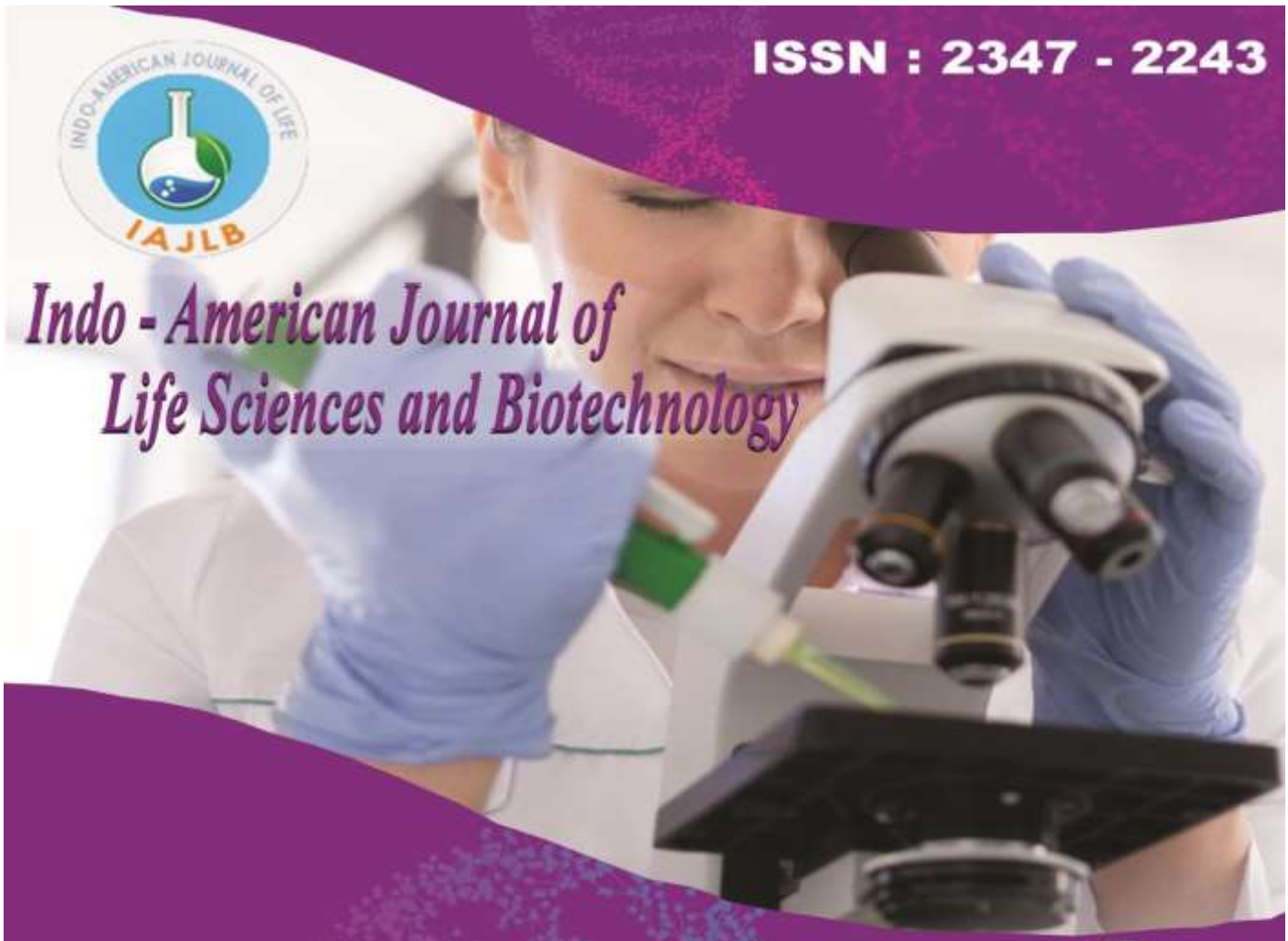

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The IPWG discusses the challenges and opportunities facing the pharmacogenomics industry.

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Abstract

Genomic data has been increasingly used by the pharmaceutical industry in the identification of therapeutic targets and the development of precision medicine strategies. Large pharmaceutical corporations often acquire DNA samples from trial participants and undertake pharmacogenomic (PGx) investigations as part of their standard operating procedure. However, there are several obstacles to implementing PGx trials throughout clinical development. Among these obstacles include the need to respond to a globally regulatory climate that is in a perpetual state of flux, difficulties in research design and clinical execution, and rising worries about patient privacy. The availability of massive genetic databases connected to patient health information, the rising usage of polygenic risk scores, and the direct sequencing of participants in clinical trials are all examples of how advances in genomics are creating new possibilities for pharmaceutical firms. Companies in the pharmaceutical industry that are involved in pharmacogenomics work together as part of the Industry Pharmacogenomics Working Group (I-PWG). Here, the I-PWG offers a bird's-eye view of the initiatives being undertaken by the pharmaceutical industry to meet these difficulties and seize new scientific openings.

Introduction

It is now common practice for pharmaceutical firms to gather DNA samples from trial participants, particularly in preliminary stages of clinical studies. However, there are a number of obstacles that businesses may encounter while adopting PGx research, ranging from the ever-changing global regulatory framework to rising concerns about patient privacy and data access. Meanwhile, recent breakthroughs in genetics have opened up exciting new avenues for PGx study. Due to the dramatic drop in price of high-throughput sequencing and genotyping over the last several years, businesses frequently do complete genetic profiling of clini- cal trial participants. An increasing amount of patient health and genetic data is being stored in large databases, making these records invaluable tools for the pharmaceutical industry. These databases may be used for both the discovery of new targets and a more in-depth analysis of already discovered ones. An organization of pharmaceutical industry professionals, the Industry Pharmacogenomics Working Group (I-PWG) company that is now engaged in the area of pharmacog-enomics. Each year, the 26 member companies that make up the I-PWG conduct hundreds of clinical studies that need DNA collection as part of their procedures. This I-PWG viewpoint aims to provide an overview of the opportunities and threats that pharmaceutical firms encounter in the area of clinical pharmacogenomics (PGx). Future clinical trials may benefit from industry-sponsored PGx investigations if researchers and regulators collaborate to resolve the problems mentioned in this viewpoint while also taking advantage of new scientific prospects.

Pharmaceutics

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Recent breakthroughs in science: sequencing participants in PGx clinical trials

Companies commonly do extensive genetic characteriza- tion of individuals in clinical trials due to the declining costs of high-throughput sequencing and genotyping in recent years. According to an unpublished 2017 survey of I-PWG members, almost 80% of member businesses reported employing next-generation sequencing (NGS) technologies for internal PGx investigations (in at least one study), and more than a third of member companies were using these technologies extensively. There were 53 percent of firms that said they used NGS for whole-genome sequencing and 71 percent that said they used it for whole-exome sequencing in clinical trials. Companies claimed that NGS technologies were being employed for PGx investigations in a wide variety of non-oncology therapeutic areas, including as cardiology, neurology, immunology, and rare disorders, however cancer was by far the most common use. Incorporating next-generation sequencing (NGS) into clinical trial samples enables a more in-depth genomic examination of trial participants and, perhaps, a more expansive study for PGx analysis that takes into account both common and unusual genetic variation (Schwarz et al. 2019).

Problems with Global Regulations for Clinical PGx Studies

The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) both recommend collecting DNA samples for PGx evaluation throughout all phases of clinical development (EMA 2018; FDA 2013), but this is not always possible due to global laws and regulations or the opinions of individual Investigational Review Boards and Independent Ethics Committees (IRB/IEC). Companies conducting worldwide clinical trials must comply with a complicated set of standards governing the collection and use of DNA and generated data for PGx research. Completely Extra! The laws, rules, and recommendations that have an effect on PGx studies are included in Table S1. This chart is not comprehensive, but it does include a substantial portion of the nations and regulations that are most often faced by sponsors.

Obtaining DNA samples or conducting genetic research is prohibited by law in several nations. The collection, maintenance, use, or provision of China's human genetic resources to foreign organizations, for instance, are all regulated under the country's Regulation of Human Genetic Resources. This rule was modified in 2019 to increase the severity of punishments for noncompliance and to further clarify the expanded scope of actions that fall within the purview of monitoring. In actuality,

Multinational corporations have been asked to provide information on the assay, vendor, and contract for carrying out genetic testing. These rules might also necessitate conducting tests on Chinese subjects inside China, which could increase the assay variability of global research. When combined, these rules might make it difficult for businesses to export samples or even gather them in the first place for future use. In addition, the law mandates that the Chinese partner get ownership of any IP developed throughout the course of the research collaboration (i.e., the clinical site in China). In addition, in October of this year, China enacted a new Biosecurity Law that aims to further strengthen the standards established in the control of genetic resources. Companies are still trying to figure out how this new rule will affect them, but in the meantime, it's making it harder than ever to gather biospecimens and evaluate people's DNA, which might slow the progress of pharmacogenomic research in China.

Resolution 340/2004 (NHC 2004) pertaining to genetic research and Resolution 2201/2001 on biorepository and biobank requirements have implications for the conduct of genetic research and storage of genetic specimens, including the requirements to share any biobanked samples with investigators in Brazil. Specific duties for the conduct of clinical trials with genetic research components are outlined in the Israeli government's Guideline for Clinical Trials in Human Subjects (2006). This may include an extra approval procedure dedicated only to the genetic research component. Last but not least, several nations have biobanking regulations that affect a company's capacity to biobank genetic material for research (e.g., Taiwan (MoHW 2019), Sweden (Regerings- kansliet 2002), and Finland (MoSAH 2012)).

Further complicating matters is the fact that different laws and regulations in various parts of the world address the issue of an individual's right to access their own genetic information that is derived from these samples. Research participants in Brazil, for instance, are guaranteed access to their genetic data, informed consent, and genetic counseling upon request according to Resolution 340/2004. Access to genetic information is also guaranteed under the Biomedical Research Law 14/2007 of Spain and by Italy's General Authorization No.8/2014 (IDPA 2014) for the processing of genetic data. Data privacy laws exist in some countries that grant citizens access to their own personal information, which may include genetic research results; examples of such countries include Norway (2000) and Argentina (2000). More generally, the EU General Data Protection

Regulations (GDPR) also grants citizens access rights to personal data (GDPR 2016). In addition, several regional and national ethical bodies have taken stands on the repatriation of inci- dental results. Research ethics regulations in Denmark have been established by the National Committee on Health Research Ethics (NVK). that uses whole-genome sequencing and requires therapeutically relevant data to be sent to participants proactively if they wish to have it returned to them (NVK 2020). Similarly, the Ethics Committee for Clinical Research (CEIC) in Portugal has established guidelines for dealing with unexpected results from genetic testing in the course of clinical studies.

Returning genetic information to people who participated in clinical trials is a complicated process, the details of which have been covered at length elsewhere (Downey et al. 2018; MRCT-Center 2017; Prucka et al. 2015). It is important to remember that providing individual genetic data to participants and their healthcare practitioners may be unethical and illegal in PGx research that is being undertaken for exploratory reasons (Thorogood et al. 2019). Analytical and clinical validity standards for diagnostic testing are not often met by the research-grade assays typically used in PGx studies. Quality standards for the testing of human specimens in laboratories for the purposes of disease diagnosis, prevention, and treatment were set, for instance, in the United States by the Clinical Laboratory Improvement Amendments (CLIA) (CLIA 2003). No clinical decision should be made based on genetic research data that were not generated in a CLIA-certified lab and did not fulfill proper analytical criteria. These results should be seen as exploratory in nature (MRCT-Center 2017). Since most clinical studies rely on underpowered exploratory research, it is important to think about how to interpret the data. While progress has been made, sponsors still face a minefield when trying to decide if, when, and how genetic data from worldwide trials should be returned to participants.

Disparities in the use of con-

Challenges for using PGx techniques in global research include the duct of PGx studies and even local variances in IRB/ EC requirements and preferences. Because of these variations, it may be difficult to manage and keep track of things like informed consent agreements, data needs, and constraints on sample usage. Although the significance of these regional requirements is recognized, the administrative effort required to handle them may discourage the collection and use of PGx samples from certain locations, thereby compromising analytical rigor and the transferability of results to other areas. We think the scientific and regulatory community can overcome some of the difficulties caused by this complexity and help forward vital genetic research.

Clinical development pitfalls for PGx analysis

Clinical trial data genetic analysis may serve as a foundation for better decisions across the clinical development life cycle, opening up new avenues for patient classification and commercialization of therapeutic value propositions (Nelson et al. 2016). However, doing genetic analysis during clinical development presents a number of obstacles and constraints, including as small research sizes, lack of worldwide representation, and issues in validating results.

To begin, the majority of clinical trials do not prioritize testing a genetic and/or PGx hypothesis. The primary goal of a study is to test a treatment hypothesis, and its power is calculated so that any differences in safety and effectiveness may be detected. Except when data from numerous trials are combined, phase I studies seldom have enough participants to perform even candidate variant analysis (Guo et al. 2019; Kobie et al. 2019). It is common for genome-wide association studies to be underpowered, especially in bigger phase II and phase III research.

One such difficulty is the general lack of variety in clinical trial populations. Most people who take part in clinical trials are of European descent (FDA 2017). The existing corpus of research in genetics is limited by this imbalance, and it is not specific to genetic analysis performed in clinical trials (Popejoy and Fullerton 2016). However, key signals may be overlooked in clinical practice if global genetic diversity is not effectively captured in PGx investigations. In fact, non-European groups either lack or have much greater frequencies of numerous recognized clinically important PGx indicators. Certain East Asian and South Asian populations have the HLA-B*15:02 allele, which is linked to skin responses to carbamazepine and oxcarbazepine (Phillips et al. 2018). Another case in point: Asians seem to have a greater prevalence of the CYP2C19 poor metabolizer phenotype, which is linked to varying degrees of medication toxicity and ineffectiveness (Scott et al. 2012). The inability to identify such relationships depends on the inclusion of a sufficiently broad sample of the population. Furthermore, when the number of participants from whom to draw conclusions is small, assessing the applicability of results from a genetic association study of drug response done in a dataset dominated by people of European ancestry to other (non-European) groups may be difficult.

Lastly, the information gathered from early clinical development programs is probably the first and only information available for new chemical entities and/or medications with unique mechanisms.

Therefore, it is difficult to validate or deny fresh genetic discoveries until further clinical trials have been undertaken. However, it may be difficult to interpret PGx data from subsequent clinical trials because to changes in clinical trial design, population heterogeneity, and a lack of statistical power for replication (Hopewell et al. 2019; Shen et al. 2020). The danger of an uninterpretable, unconfirmable exploratory discovery may exceed the upside potential, and this ambiguity in interpreting therapeutic usefulness for genetic analysis during drug development is a general barrier for commencing exploratory research.

Studying the ADME of PGx is not without its difficulties.

The majority of the known PGx correlations may be attributed to genetic variations that cause changes in drug metabolizing enzymes and drug transporters (FDA 2015; Tremaine et al. 2015). Such variations might affect medication safety or effectiveness because they modify enzyme or transporter function, resulting in inter-individual variability in exposure that can go beyond the therapeutic window for small molecules. There are a number of obstacles that are particular to PGx research in early phase studies, in addition to the problems with small clinical trial sizes that we've already covered. Emergence of novel variations with clinical importance, and the possibility of ambiguity in defining metabolic routes for new medicines in early clinical development, are two examples. To maximize the likelihood of success when conducting analyses in very small trial datasets, PGx studies in early phase studies should be conducted in a targeted manner, giving higher priority to variants in genes that have been shown via preclinical work to be important for the disposition of the compound. However, major and minor metabolic pathway investigations in vitro are generally not finished prior to phase II or even pivotal trials in humans. Therefore, it is generally necessary to combine as much PK data from early phase clinical trials as feasible to increase statistical power and evaluate a larger group of ADME genes. The population PK modeling estimates of PK parameters from bigger phase II/III studies may also be utilized to evaluate the possible effect of variations in ADME genes (Guo et al. 2019; Kobie et al. 2019). However, it's possible that these data sets don't have enough statistical power to discover genetic connections. In instance, individuals may have more than one functional mutation in a set of metabolizing enzymes, which makes it difficult to find uncommon variations that potentially alter safety exposure. Drugs that are primarily metabolized by highly polymorphic Cytochrome P450 enzymes (CYPs) like CYP2D6 have been largely phased out of use in recent decades as rational drug design has shifted focus to maximizing the distribution of drug metabolism across many CYPs and other enzyme families. Even yet, the possibility is not completely nullified possibility that a patient's exposure will vary due to the presence of a poor metabolizer phenotype in two of those enzymes. Studies of PGx have also shown promise in illuminating the potential importance of other metabolic clearance pathways, such as glucuronidation and the function of membrane transporters (Desai et al. 2003; Guillemette 2003; Yee et al. 2018). PGx investigations may be necessary to understand the possible influence of genetic polymorphisms in these other groups of metabolic enzymes or in membrane transporters on PK and pharmacodynamics, despite the typically weaker previous clinical data supporting their functional impact.

Genotyping for ADME genes should be performed in both early and late stage clinical trials, and it is advised that the metabolic pathways of all incoming clinical candidates be thoroughly evaluated. It is reasonable to investigate the possible impact during NCE development if the medication is metabolized via pathways with known polymorphism variation and there is substantial evidence suggesting clinically important effects for other authorized agents in the same class. When there is unexpected PK variability that cannot be explained by standard PGx genotyping, the European Medicines Agency (EMA) has issued PGx recommendations that suggest the possible use of wider, whole-exome or whole-genome sequencing to investigate potential new vari- ants (EMA 2018). Additional difficulties arise with more comprehensive genome sequencing, such as the potential requirement for regulatory authorities to demand phenotypic confirmation of new variations.

Clinical implementation challenges

The number of clinically relevant indicators that might be used to enhance patient care is rising (FDA 2015; Relling et al. 2020), however despite the commitment of resources by business and academia in developing PGx biomarkers, such information is still not frequently employed in clinical practice. Many factors contribute to this; these have been reviewed at length elsewhere (Chenoweth et al. 2020; Klein et al. 2017) and include, but are not limited to, challenges with ordering, reimbursement, and interpretation of genetic tests; a lack of education for both patients and clinicians; and limited evidence supporting the clinical utility and health economic value of many PGx bio-markers. Further, it has been found that different regulatory agencies for the same drug have different recommendations for PGx testing included in drug labels (Koutsilieri et al., 2020; Shekhani et al., 2020), suggesting that the lack of consensus guidelines for genetic testing and implementation may be an additional barrier for clinicians attempting to incorporate PGx information into clinical practice.

The obstacles to clinical implementation have been studied and attempts made to remove them. Organizations

such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) and

For clinical use of PGx data, the Dutch Pharmacogenomics Working Group (DWPG) has developed recommendations (Bank et al. 2018). Some hospitals and healthcare networks have begun doing pre-emptive PGx testing (Cecchin et al. 2017, Dunnenberger et al. 2015) so that doctors don't have to wait for test results before giving medicine. For certain commonly prescribed medications, studies have been conducted to establish the clinical validity, utility, and economic worth of PGx biomarkers (Anderson et al. 2007; Claassens et al. 2019; Pereira et al. 2020; Wadelius et al. 2009; Zhu et al. 2020). However, genetic testing are still not widely used in clinical practice, and the lack of a PGx companion diagnosis is often seen as a major roadblock in the pharmaceutical industry. Industry's emphasis on and investment in PGx research is projected to increase as PGx data gradually finds its way into clinical practice.

It's important to remember that environmental, anthropometric, and genetic variables, as well as biological subsystems impacted by the illness, may all interact to produce a medication response that is very complicated in many circumstances (Armstrong 2008). This means that the use of genetic markers, biomarkers, and other single stratifying factors is likely to be constrained by the fact that no one factor is likely to capture the entire extent of the complexity involved and provide sufficiently accurate predictions for therapeutic use. This motivates researchers to look into novel avenues, such as polygenic risk scores (discussed further below) and machine learning techniques, for further progress in the area. Increases in processing capacity and the development of machine learning algorithms have made it possible to combine different forms of data for a more complete picture of a patient's reaction to a treatment, leading to greater accuracy in predictions and easier clinical translation.

Polygenic risk ratings in PGx research: a new frontier

The use of polygenic risk scores to PGx research is a hot new topic in the field. The use of polygenic risk scores for coronary artery disease (CAD) precision medicine has been recommended by a number of research. Patients with higher CAD polygenic risk scores have been shown to benefit more from statin therapy, according to two meta-analyses (Mega et al. 2015; Natarajan et al. 2017). Patients with high polygenic risk scores for coronary artery disease had more clinical benefit from therapy with PCSK9 inhibitors in two large, independent retrospective investigations (Damask et al. 2020; Levin and Rader 2020; Marston et al. 2020). Likewise, polygenic risk scores have been investigated in the prevention of atherothrombotic events. In a retrospec- tive PGx study of clopidogrel, Lewis et al. identified a poly- genic risk score that was associated with increased platelet reactivity, risk of developing major adverse cardiovascular events, and risk of cardiovascular death (Lewis et al. 2020). Finally, in the field of oncology a recent study found that high vitiligo, high psoriasis, and low atopic dermatitis polygenic risk scores were associated with longer overall survival after treatment with atezolizumab (anti-PD-L1) monotherapy compared to treatment with chemotherapy in bladder cancer patients (Khan et al. 2020).

Patient enrolment in clinical trials may be improved with the use of polygenic risk ratings. It is possible for people with high polygenic risk scores to have illness risk equivalent to that seen in those with monogenic disorders (Khera et al. 2018). There is a possibility that clinical trial sizes may be reduced or the length of event-driven studies could be shortened if individuals with high polygenic risk scores were included selectively. Although the association between polygenic risk scores and treatment response is a relatively new topic of inquiry in drug development, it is expected to garner increasing scientific attention across a wide variety of illnesses and therapeutic domains in the future.

Applying methods like polygenic risk scores and machine learning to patient selection tactics in clinical research has regulatory ramifications, including potential effects on medication labeling and the necessity for a companion diagnosis. As a result, once a medicine is authorized, regulatory agencies want to know that there is a reliable way to identify the patients who would get the most benefits from it and that the label appropriately represents the enrichment tactics used to choose them. Regular communication with regulatory agencies throughout medication development is essential, as is consideration of the impact of enrichment tactics on labeling and the path to approval of any test intended as a companion diagnostic (FDA 2019).

Patients with common cancers and their families in the NHS, as well as those with rare diseases and their families substances currently available on the market (Diogo et al. 2018; McInnes et al. 2020). The success rates of drug development projects are higher when the medication target has genetic proof to back it up

(Nelson et al. 2015). It's possible that various types of genetic variation might provide light on potential therapeutic targets. In particular, LOF variations have attracted a lot of attention because of their potential as therapeutic targets. When this kind of genetic polymorphism is protective against illness risk, it may analagize to the actions of therapeutic antagonists (like PCSK9) (Cohen et al. 2006). Phenomenon-wide association studies (PheWAS) inside these massive datasets may characterize pharmacological targets to find new indications, related indications, or even possible safety flags (Diogo et al. 2018; Jerome et al. 2020). Additional evidence in favor of variations found by PGx analysis of current clinical trials for medications in development may be gathered from the material included in these huge databases. In conclusion, unique genetic patient subpopulations may be discovered for precision medicine clinical development programs or for call back studies to do further in-depth patient phenotyping.

Summary

Pharmaceutical corporations have already invested extensively in genomic technology, databases, and PGx research, and this trend will only accelerate. From initial target identification through late-stage clinical development, genomics is now an essential aspect of the drug development process. Although the difficulties highlighted here are substantial, they will be overcome as pharmaceutical firms increasingly use precision medicine tactics across the drug development process. One of the biggest obstacles to doing international research is the ever-evolving legal and regulatory framework in which such studies must be conducted. Worries, while

While worries about patient privacy and the exploitation of patient data are warranted, too restrictive laws would stifle progress in PGx discoveries and, by extension, precision medicine for the world's populations as a whole. Positively, developments in genomic technology are accelerating, and pharmaceutical firms are adapting to the new landscape. In the next years, clinical trial PGx investigations will likely benefit from the addition of patient-level sequencing, polygenic risk scores, and data from massive electronic health record (EHR)/genomic databases to seed their results.

References

Barton S, Nicholas ZP, Kahn SF, May HT, Samuelson KM, Muhlestein JB, Carlquist JF, Couma-Gen I, Grove AS, Stevens SM, Horne BD, Kahn SF, Muhlestein JB, Carlquist JF, Couma-Gen I. (2007) A randomized controlled trial comparing genotype-guided warfarin dosing with conventional dosing in patients starting oral anticoagulation. In the journal Circulation, 116, pages 2653-2570. Argentina's Personal Data Protection Act of 2000 may be found at http://www.jus.gob.ar/media/3201023/personal_ data protection act25326.pdf if you're interested in reading more about it. Date Accessed: March 8, 2021

To cite: Armstrong, M. (2008) What we know about the genetics of medication responses that go wrong. Included in: Pharmacogenomics and precision medicine. The authors (PCD Springer, KE Caudle, JJ Swen, RS Gammal, MW Whirl-Carrillo, TE Klein, MV Relling, HJ Guchelaar) (2018) Guidelines from the Dutch Pharmacogenetics Working Group and the Clinical Pharmacogenetics Implementation Consortium: a comparison. Clinical Pharmacotherapy. 103:599-618. https://doi.org/10.1002/cpt.762

Ubiquitous Pharmacogenomics Consortium; Cecchin E., Roncato R., Guchelaar H.J., Toffoli G. (2017) The moment has come to fully embrace ubiquitous pharmacogenomics (U-PGx). To accelerate the incorporation of pharmacogenomics into clinical practice, Horizon 2020 has been established. There are 18 issues of the journal "Current Pharmaceutical Biotechnology" that range from 204 to 209. https://doi.org/10.2174/138920101866617 \s0103103619

The authors (Chenoweth MJ, Giacomini KM, Pirmohamed M, Hill SL, van Schaik RHN, Schwab M, Shuldiner AR, Relling MV, and Tyndale RF) (2020) Pharmacogenomics and precision medicine on a global scale: obstacles and prospects. Clinical Pharmacology and Therapeutics 107:57–61. Click here to access the DOI: 10.1002/cpt.1664

According to the authors (in alphabetical order): Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, Van' t Hof AWJ, van der Harst P, Barbato E, Morisco C, Tjon Joe Gin RM, Asselbergs FW, Mosterd A, Herrman JR, Dewilde WJM, Janssen PWA, Kelder JC, Postma MJ, de Boer A (2019) P2Y12 inhibitors as first-line therapy for primary pulmonary hypertension: a genotype-guided oral approach. Journal of the New England Medical Center 381(16):1621-1631. https://doi.org/10.1056/NEJMoa1907096

CLIA (2003) (2003) To read Section 263A of Title 42 of the United States Code, go here: https://www.govinfo.gov/content/pkg/USCODE-2011-title42/pdf/USCODE-2011-title42-chap6A-subchapII-partF-subpa rt2-sec263a.pdf. Date Accessed: March 8, 2021

Reference: Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH (2006) Protective effects of low LDL levels and PCSK9 sequence variants against coronary heart disease. The New England Journal of Medicine. URL: https://doi.org/10.1056/NEJMoa054013

Overton JD, Lotta LA, Yanco- poulos GD, Abecasis GR, Baras A, Paulding C, Regeneron Genet- ics C, the OOI, Damask A, Steg PG, Schwartz GG, Szarek M, Hagstrom E, Badimon L, Chapman MJ, Boileau C, Tsimikas S, Ginsberg HN, Banerjee P, (2020) In the ODYSSEY OUTCOMES Trial, alirocumab therapy may have a larger therapeutic benefit for patients with high genome-wide polygenic risk scores for coronary artery disease. 141:624-636 in the journal Circulation. To cite this article: https://doi.org/10.1161/CIRCU LAT NAT AHA.119.044434

AA Desai, F. Innocenti, and MJ Ratain (2003) Pharmacogenom- ics of uridine deiminase (UGT) and its relevance to cancer risk and treatment.

Pharmacogenetics, 13, 517–523, DOI: 10.1097/01.fpc.000054116.14659.e5.

Balasubramanian S, Abul-Husn NS, Hartzel DN, Lavage DR, Kost KA, Packer JS, Lopez AE, Penn J, Mukherjee S, Gosalia N, Kanagaraj M, Li AH, Mitnaul LJ, Adams LJ,

Person TN, Praveen K, and Praveen S. (2016) Functional variations in 50,726 whole-exome sequences from the DiscovEHR study: distribution and clinical effect. Retrieved from "https://doi.org/10.1126/science.aaf6814" by

Hutz J, Reeve M. P., Bing N., John S., MacArthur D. G., Salomaa V., Ripatti S., Hako- narson H., Daly M. J., Palotie A., Diogo D., Tian C., Franklin C. S., Alanne-Kinnunen M., March M., Spen- cer C. C. A., Van (2018) In order to validate pharmacological targets, it is necessary to conduct phenome-wide association studies in large population cohorts. Nat Commun. 9.4285. Doi: 10.1038/s41467-018-06540-3

A.S. Downey, E.R. Busta, M. Mancher, and J.R. Botkin (2018) New Research Strategies for Disseminating Individual Results to Participants. Downey A.S., E.R. Busta, M. Mancher, and J.R. Botkin (eds) Committee on the Return of Individual-Specific Research Results Generated in Research Laboratories. Health and Medicine Division, Board on Health Sciences Policy, National Academies of Sciences, Engineering, and Medicine. Washington, DC: National Academies Press (USA) (DC). Check it out: https://doi.org/10.17226/25094

Howard SC, Hunkler RJ, Caudle KE, Broeckel U, Dunnenberger HM, Crews KR, Hoffman JM, Caudle KE, Klein TE, Evans WE, Relling MV (2015) Current efforts for anticipatory clinical pharmacogenetics in five US medical facilities. 55, pp. 89-106 in the annual review of pharmacology and toxicology. Obtainable at: https://doi.org/10.1146/annurev-pharm tox-010814-124835

EMA (2018) (2018) Effective use of pharmacogenomics.

Labeling and premarket review in early-phase clinical trials under the FDA's 2013 guidance for industry clinical pharmacogenomics. Federal Health and Human Services Administration, Silver Spring, USA

FDA (2015) (2015) Pharmacogenomic biomarkers in drug labeling, presented in a table. Table of pharmacogenomic biomarkers on medicine labels, available at https://www.fda.gov/drugs/science-and-research-drugs.

Date Accessed: March 8, 2021

Clinical Trials Global Participation Report, 2015–2016, FDA (2017). FDA (2019) (2019) Clinical trial enrichment procedures to help determine the efficacy of human pharmaceuticals and biological goods.

GDPR (2016) (2016) the EU's General Data Protection Regulation (GDPR). GDPR Information Portal: https://gdpr-info.eu.

Author: Guillemette C. (2003) The pharmacogenomics of UDP-glucuronosyltransferase enzymes in humans. Journal of Pharmacogenomics 3:36-158. URL: https://doi.org/10.1038/sj.tpj.6500171

The authors (in order) are: Guo Z, Caro L, Robertson MN, Hwang P, Hoover P, Wudarski C, Mai- uri K, Wang YH, Mogg R, Mehrotra DV, Blanchard R, Shaw PM, and Blanchard R. (2019) Effects of OATP1B1 variations on the pharmacokinetics and therapeutic value of elbasvir/grazoprevir: a pharmacogenetics analysis. Reference: 20:631-641 in the journal Pharmacogenomics. "pgs-2019-0022" may be found online at https://doi.org/10.2217/ pgs-2019-0022

Annotated Bibliography: Hopewell JC, Ibrahim M, Hill M, Shaw PM, Braunwald E, Blaustein RO, Bowman L, Landray MJ, Sabatine MS, Collins R (2019) Response to anacetrapib depends on ADCY9 genotype, according to a study published in Circulation. To cite this article: https://doi.org/10.1161/CIRCULATIONAHA.119.041546

IDPA (2014) Access this document at https://www.garanteprivacy.it/home/docweb/-/docweb-display/docweb/3786078.

To cite this article: Jerome RN, Joly MM, Kennedy N, Shirey-Rice JK, Roden DM, Bernard GR, Holroyd KJ, Denny JC, Pulley JM (2020) Making use of human genetics to spot warning signs before medication approval and clinical usage. Drug Safety.43(9):567582. Here's the scholarly citation: https://doi.org/10.1007/s40264-020-00915-6

The authors of this paper are: Khan Z, Di Nucci F, Kwan A, Hammer C, Mariathasan S, Rouilly V, Carroll J, Fontes M, Ley Acosta S, Guardino E, Chen-Harris H, Bhangale T, Mellman I, Rosenberg J, Powles T, Hunkapiller J, Chandler GS, Albert ML (2020) Immune checkpoint inhibition in bladder cancer is affected by polygenic risk for cutaneous autoimmunity. Science (Proc Natl Acad USA) 117:12288-12294. Click here to get the DOI: 10.1073/pnas.1922867117

Genome-wide polygenic scores for common illnesses identify people with risk equal to monogenic mutations. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, Natarajan P, Lander ES, Lubitz SA, Ellinor PT, Kathiresan S (2018). Science (Nat. Genet.) 50:1219–1224. https://doi.org/10.1038/s41588-018-0183-z

"Klein M.E., M.M. Parvez, and J.G. Shin" (2017) Clinically using pharmacogenomics for precision medicine at the individual level: challenges and opportunities. Journal of Pharmaceutical Science. 106(9):2368-2379. For further information, please visit: https://doi.org/10.1016/j.xphs.2017.04.051

Shaw PM, McCrea JB, Blanchard R, Menzel K, Kobie J, Guo Z, Cho CR, Menzel K, and Kobie, Blanchard, and Blanchard (2019) Analyzing the effects of OATP1B1, UGT1A1, and BCRP variations on the pharmacokinetics of leter- movir in prior clinical investigations. 1236-1243 J Clin Pharmacol. https://doi.org/10.1002/jcph.1420

Patrinos GP, Sismanoglou DC, Koutsilieri S, Tzioufa F. (2020) Bringing to light the regulatory and research consortia's divergent recommendations for drug treatment interventions informed by genomic data. 153, 104590, Pharmacol. Res. You may find the paper here: https://doi.org/10.1016/j.phrs.2019.104590

MG Levin & DJ Rader (2020) Ready for prime time? Polygenic risk scores and coronary artery disease. To be published in Circulation, page numbers should read 141:637-640. Here's the scholarly citation: https://doi.org/10.1161/CIRCULATIONAHA.119.044770

Kim EY, Aradi D, Fer- nandez-Cadenas I, Lee MTM, Whaley RM, Montaner J, Gensini GF, Cleator JH, Chang K, Holmvang L, Hochholzer W, Roden DM, Winter S, Altman RB, Alexopoulos D, Kim HS, Gawaz M, Bliden

KP, Valgimigli M, Marcucci R, Campo G (2020) Ischemic events and cardiovascular death in clopidogrel-treated individuals may be predicted using a pharmacokinetic polygenic response score. 203–210 in the European Journal of Cardiovascular Pharmacology and Therapeutics. Use this link to access the article: https://doi.org/10.1093/ehjcvp/pvz045

Ruff CT, Giugliano RP, Lubitz SA, Ellinor PT, Sabatine MS, Ruff NA, Kamanu FK, Nordio F, Gurmu Y, Roselli C, Sever PS, Pedersen TR, Keech AC, Wang H, Lira Pineda A, Keech AC, Giugliano RP, Lubitz SA, Giugliano RP, Lubitz SA, Giugliano RP (2020) Evidence from the FOURIER study suggests that a genetic risk score may be used to predict whether or not individuals with atherosclerotic disease would benefit from treatment with evolocumab. 141(:616)623 of Circulation. Use this citation: https://doi.org/10.1161/CIRCULATIO NAHA.119.043805

McInnes, G.; Lavertu, A.; Sangkuhl, K.; Klein, T. E.; Whirl-Carrillo, M.; Altman, R. B. (2020) A large-scale investigation of pharmacogenetics using data from the UK biobank. Therapeutics in Clinical Pharmacology and Physiology. https://doi.org/10.1002/cpt.2122

Super JL, Stitziel N. O., Smith J. G., Chasman D. I., Caulfield M., Devlin J. J., Nordio F., Hyde C., Cannon C. P., Sacks F., Poulter N., Sever P., Ridker P. M., Braunwald E., Melander O., Kathiresan S., Sabatine M. S.,

Genetic risk, coronary heart disease events, and the therapeutic effectiveness of statin therapy: a review of primary and secondary preventive studies. Reference: Lancet 385:2264-2271. MoHW (2019) https://law.moj.gov.tw/Eng/LawClass/LawAll.aspx? PCode=L0020164 [DOI:10.1016/S0140-6736(14)61730-X]. 8 March 2021 https://finlex.fi/en/laki/kaannokset/2012/en20120688.pdf> MoSAH (2012). Date Accessed: March 8, 2021

MRCT-Center Recommendations for Reporting Individual Outcomes to Study Participants (2017). Reference: https://mrctcenter.org/wp-cont e nt/uploads/2017/12/2017-12-07-Return-of-Individual-Results-Recommendations-Document-V-1.2.pdf. Date Accessed: March 8, 2021

P. Natarajan, R. Young, N. O. Stitziel, S. Padmanabhan, U. Baber, R. Mehran, S. Sartori, V. Fuster, D. F. Reilly, I. Ford, J. Rader, S. Fuster, N. Sattar, and S. Kathiresan (2017) In the primary prevention scenario, a polygenic risk score reveals a sub-group with a higher burden of atherosclerosis and a larger relative benefit from statin medication. 135(Circ.):2091-2101. This article's DOI is: 10.1161/CIRCULATIO NAHA.116.024436.

For example: "Nelson MR, Tipney H, Painter JL, Shen J, Nicoletti P, Shen Y, Floratos A, Sham PC, Li MJ, Wang J, Cardon LR, Whittaker JC, Sanseau P." (2015) Indications for prescribed drugs that are supported by human genetic data. Reference: Nat. Genet. 47:856–860. This article's DOI is: 10.1038/ng.3314.

Xu CF, Waterworth DM, Chissoe SL, Xu CF, Xu CF, Warren L, Hughes AR, Nelson MR, Johnson TM, Warren LB (2016) Potential and barriers in medication effectiveness research based on genetics. Nature Reviews Genetics 17:197-206. Retrieved from "https://doi.org/10.1038/nrg.2016.12 NHC" (2004) https://conselho.saude.gov.br/resolucoes/2004/Res340 \sen.pdf. Retrieved 8 March 2021 from NVK (2020). https://en.nvk.dk/rules-and-guidelines. Date Accessed: March 8, 2021

Hasan A, Iturriaga E, Lerman A, Sidhu M, Tanguay JF, Wang L, Weinshilboum R, Welsh R, Rosenberg Y, Bailey K, Rihal C; Pereira NL; Farkouh ME; So D; Lennon R; Geller N; Mathew V; Bell M; Bae JH; Jeong MH; Chavez I; Abbott JD; Cagin C; Baudhuin (2020) Ischemic outcomes following percutaneous coronary intervention: the TAILOR-PCI randomized clinical study comparing oral P2Y12 inhibitor selection guided by genotype to standard clopidogrel medication. JAMA 324:761–771. https://doi.org/10.1001/jama.2020.12443

Phillips, E.J.; Sukasem, C.; Whirl-Carrillo, M.; Muller, D.J.; Dunnenberger, H.M.; Chantratita, W.; Goldspiel, B.; Chen, Y.T.; Carleton, B.C.; George, A.L., Jr.; Mushiroda, T.; Klein, T.; Gammal, R.S.; Pirmo (2018) Guidelines for the use of carbamazepine and oxcarbazepine based on human leukocyte antigen genotype in clinical practice: 2017 update from the Clinical Pharmacogenetics Implementation Consortium. The citation is as follows: Clin Pharmacol Ther 103:574-581. Use this citation: https://doi.org/10.1002/cpt.1004

AB Popejoy, SM Fullerton (2016) Genetic analysis has not been successful in preserving cultural differences.

The citation for this article is Nature 538:161-164. https://doi.org/10.1038/538161a

SK Prucka; LJ Arnold; JE Brandt; S. Gilardi; L.C. Harty; F. Hong; M. Malia; D. J. Pulford; (2015) Here's the latest on the industry's pharmacog- enomics working group's thoughts on sharing people's genetic test findings with them. The Journal of Bioethical Inquiry 29:82–90. Check out this link: https://doi.org/10.1111/bioe.12073

Regeringskansliet (2002) (2002) Biobanks in medical care act (Swedish) https://biobanksverige.se/wp-content/uploads/Biobanks-in-medical-care-act-2002-297.pdf. Date Accessed: March 8, 2021

The authors (Relling MV, Klein TE, Gammal RS, Whirl-Carrillo M, Hoffman JM, Caudle KE) (2020) Putting pharmacogenetics into practice in the clinic: a decade later. The results are published in Clin Pharmacol Ther 107, pages 171–175. https://doi.org/10.1002/cpt.1651

RB Kim, UI Schwarz, and M. Gulilat (2019) Next-generation sequencing's impact on the fields of pharmacogenetics and pharmacogenomics. Journal of the American Medical Association.

Sangkuhl, K.; Scott, S. A.; Shuldiner, A. R.; Hulot, J. S.; Thorn, C. F.; Altman, R. B.; Klein, T. E. (2012) PharmGKB's synopsis of the cytochrome P450, family 2, subfamily C, polypeptide 19 pharmacogene. Pharmacogenet. Genomics. 22(9):159-165. Use this citation: https://doi.org/10.1097/FPC.0b013e32834d4962

Shekhani, R., L. Steinacher, J.J. Swen, and M. Ingelman-Sundberg (2020) Opportunities for better pharmacogenomic medication labeling regulation and recommendations. Clinical Pharmacology and

Therapeutics 107:1255.1250. https://doi.org/10.1002/cpt.1720
Nickle D, Hol- zinger ER, Chhibber A, Wilcox MH, Blanchard RL, Shaw PM, Shen J, Mehrotra DV, Dorr MB, Zeng Z, Li J, Xu X (2020) The use of bezlotoxumab to treat clostridium difficile infection is associated with protection against reinfection due to a genetic factor. In mSphere. DOI: 10.1128/mSphere.00232-20
Spain (2007) (2007) Spanish Law on Biomedical Research in English (https://www.isciii.es/QueHacemos/Financiacion/solicitudes/Documents). Date Accessed: March 8, 2021
There are a lot of people that contributed to this paper: Szustakowski JD, Balasubramanian S, Sasson A, Khalid S, Bronson PG, Kvikstad E, Wong E, Liu D, Davis JW, Haefliger C, Loomis AK, Mikkilineni R, Noh HJ, Wadhawan S, Bai X, Hawes A, Krasheninina O, Ulloa R (2020) Through exome sequencing of the UK biobank, we can further human genetics studies and medication discovery. medRxiv. https://doi.org/10.1101/2020.11.02.20222232
A. Thorogood, G. Dalpe, and B.M. Knoppers (2019) If you do genetic research on an individual, would you be required to return your data? Journal of the European Society of Human Genetics 27(4):534-546. URL: https://doi.org/10.1038/s41431-018-0311-3
Marshall JC, Johnson K, Li L, Pearson K, Tremaine L, Brian W, DelMonte T, Francke S, Groenen P, Li L, and Tremaine JC (2015) ADME pharmacogenomics' impact on Phase I clinical trials from the viewpoint of the Industry Pharmacogenomics Working Group (I-PWG). Pharmacogenomics, 16, p. 2055–2067. https://doi.org/10.2217/pgs.15.141
Liu D, Pandey AK, Gonzaga-Jauregui C, Khalid S, Ye B, Banerjee N, Gonzaga-Jauregui C, Van Hout CV, Tachmazidou I, Backman JD, Hoffman JD,

Authors: Li AH, O'Dushlaine C, Marcketta A, Staples J, Schurmann C, Hawes A, Maxwell E, Barnard L, Lopez A, Penn J, Habegger L, Blumenfeld AL, Bai X, O'Keeffe S, Yadav A, Praveen K, Jones M, Salerno WJ, Chung WK, Surakka I, Willer CJ, Hveem K, Leader (2020) Analysis of 49,960 UK Biobank participants using exome sequencing and characterisation. The scientific report of Nature 586:749–756. Doi: 10.1038/s41586-020-2853-0
Deloukas, P.; Rane, A.; McGinnis, R.; Holm, L.; McGinnis, R.; Rane; and Wadelius, M.; Chen, Y.; Lindh; J.; Eriksson; N.; Ghori, M.; Bump, S. (2009) Genetic prediction is supported by the largest prospective cohort of warfarin patients. Blood 113:784-792. The citation for this article is: https://doi.org/10.1182/blood-2008-04-149070.
Yee S.W., D.J. Brackman, E.A. Ennis, Y. Sugiyama, L.K. Kamdem, R.B. Chard, A. Galetin, K.M. Blan- chard, and L. Zhang and K.M. Giacomini (2018) Drug disposition and response as influenced by transporter polymorphisms: an international consortium's point of view. Clinical Pharmacology & Therapeutics 104:803-817. https://doi.org/10.1002/cpt.1098
St. Sauver JL, Visscher SL, Prokop LJ, Bielinski S.J., Wang L., Weinshilboum R., Borah B.J., Zhu Y. (2020) Pharmacogenomics-guided therapy for cardiovascular diseases: a systematic evaluation of the evidence for cost-effectiveness. The journal Genet. Med. To cite this article: https://doi.org/10.1038/s41436-019-0667-y
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