Roadmap to Drug Development Enabled by Pharmacogenetics

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Abstract The primary goal of the pharmaceutical industry is to develop safe and effective medications. As the industry matures and the existing arsenal of marketed therapeutics grows, novel drugs must exhibit greater efficacy and safety to achieve registration and favorable reimbursement. Furthermore, gaining market-share has become extremely competitive, in terms of both meaningful clinical effects and tolerated safety profiles. As a result, the pharmaceutical industry has experienced a steady decline in productivity in recent decades. However, the achievement of regulatory approvals for targeted therapeutics may reverse this drop in productivity. The convergence of high-throughput genetic analysis technologies and the exponentially expanding biological and genomic knowledgebase have provided many clear examples that genetic variation can affect both disease risk and drug response. Therefore, evaluation of genetic variation in clinical trial populations should be considered essential and routine from the earliest phases of drug development. Pharmacogenetics (PGx) in particular has gained considerable attention from drug developers, regulators and payers over the past decade as a means to achieving safer, efficacious and more cost-effective drugs. While PGx science has great potential to impact positively the success of developing a new medicine, the integration of PGx into the decision making processes of the drug development pipeline has been difficult. The goal of this chapter is to describe the principles and requirements of an efficient

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G. Grech, I. Grossman (eds.), *Preventive and Predictive Genetics: Towards Personalised Medicine,* Advances in Predictive, Preventive and Personalised Medicine 9,
DOI 10.1007/978-3-319-15344-5_3

and valuable PGx strategy that makes use of every opportunity during the course of developing innovative medicines. This strategy combines a proven methodology with rigorous genetic science to create a "*Pipeline Pharmacogenetic Program*".

Keywords Novel drugs · Companion diagnostics · Pipeline pharmacogenetics · Clinical trials · Drug development · Project management methodology

1 Pharmacogenetics in Today's Market-Place

Consumer demand for customized products and services is well established and evident in mainstream retail markets as well as emerging technologies. Gone are the days of "one-size fits all" and if a product or service is mass produced, then the available combinations, flavors and add-ons are so numerous that most consumer experiences can be, or at least feel, truly personalized. Similar pressures exist in healthcare markets. In fact, personalized medicine has the potential to benefit the consumer more than most retail products. The complexities of health and disease, underlined by each patient's specific environmental and genetic factors, call for a truly personalized approach given the suboptimal performance of standard therapy (most drugs exhibit response rates lower than 60%) [1]. Recognizing this growing need for individualized healthcare, many USA healthcare providers and hospitals offer services through "Centers of Personalized Medicine", like the Duke University Health System, MD Anderson Cancer Center, and Cleveland Clinic. Similarly, clinical pharmacologists and medical laboratories throughout Europe provide Personalized Medicine services, including the Karolinska Medical System and the Erasmus University-Rotterdam. Furthermore, international collaborative networks on personalized medicine are quickly forming to enhance knowledge acquisition and leverage capabilities. The Personalized Medicine Coalition, for instance, consists of over 200 academic, industry, healthcare provider and payer groups "seeking to advance the understanding and adoption of personalized medicine concepts and products for the benefit of patients" [2]. The European Commission is dedicating considerable investment in Horizon 2020 for innovation across European member countries with an emphasis on personalized medicine and systems medicine [3]. A key element of Personalized Medicine concepts and products has been and will likely continue to be in the area of PGx. There are currently 128 FDA-approved drugs that contain pharmacogenomic information in their label [4]. Indeed, regulatory agencies promote using genetic information in the drug development process in order to improve safety and efficacy by using pharmacogenomics information to decrease adverse events and to identify non-responders [5]. The general public also appears to have considerable interest and willingness in PGx testing to predict side effects, guide dosing and assist with drug selection [6]. The growing genetic testing market, estimated at $ 5.9 billion in 2016, and numerous direct-to-consumer and physician-provided genetic test companies are evidence of the economic forces driving the industry [7, 8]. The need for tailored medicines and the favorable regulatory environment to facilitate their development is driving increased availability of genetic testing services, thus creating market forces that reduce the cost of acquiring individual genetic information. For example, cur-

rently the cost for whole genome sequencing is $ 5800 per sample [9]. It is therefore an unquestionable fact that Personalized Medicine has arrived and its utilization and effects on healthcare is growing. For instance, in a recent McKinsey report the authors indicate that already over a third of the drugs currently in clinical studies are associated with a companion biomarker, indicating that newly approved drugs in the coming years will increasingly be dominated by targeted therapeutics [10]. However, the process of investigating, validation and qualifying companion PGx tests is challenging. It requires early investments in scientific infrastructure, and it hinges on clear *a priori* commercial and regulatory strategies to ensure the timely and cost-effective launch of the two end-products (i.e. the drug (Rx) and the diagnostic (Dx)). In addition to the principles of an efficient and valuable PGx strategy, we outline below the requirements, advantages and challenges associated with integrating PGx investigations into the drug research and development (R&D) pipeline. The information reported is based on our deep expertise in "Pipeline Pharmacogenetics" acquired over cumulative decades of application across diverse therapeutic areas and several global pharmaceutical companies.

2 Pharmacogenetics-by-Design: the R&D Environment

The application of PGx to currently marketed drugs as a method to predict safety and efficacy is of significant value to patients, physicians, regulators, payers and industry (some examples include warfarin, abacavir and multiple oncologic agents). The inability to predict the risk of adverse drug reactions (ADR) each time a patient is exposed to a new medicine continues to dramatically affect patients' morbidity and mortality. For example, in two separate studies, researchers reported that ADRs are estimated to be the 7th most common cause of death in a 2001 Swedish population based study [11] and that the incidence of serious ADRs was estimated to be 6.7% of hospitalized patients in the US [12]. In addition, most medicines display significant inter-individual variability in efficacy, but the current clinical practice approach addresses this problem by passive and reactive empirical methodology: treatment is administered according to standard protocols and outcome is assessed during later visits to determine efficacy. This "trial and error" practice is usually followed by either dose adjustments or triage onto other medicines if the patient poorly responds or fails treatment. This practice also results in prolonged procedures, including delay of efficacious treatment (sometimes over the course of months and years in the case of immunomodulatory treatments), risk of exposure to unnecessary drugs (which are always associated with a host of side effects), protracted suffering of patients and their caregivers, and, finally, additional cost to payers.

The development of PGx tests for registered medicines aims to identify optimum benefit-risk ratios and allow prospective testing prior to administration of drug. The availability of PGx testing also permits a differentiation strategy that guides the pharma industry to develop medicines tailored specifically for non-responder populations, thus addressing true unmet medical needs. Regulatory approved PGx safety tests prospectively predict who is at risk of considerable harm and provide high value as a warning to healthcare providers and patients regarding drugs about to be launched or

currently on the market. Equally important, predicting specifically who is going to be at risk of ADRs and excluding them from treatment prevents valuable medicines from being withdrawn from the marketplace. The PGx test thus serves to identify those patients who should be administered a drug and expect meaningful efficacy and safety.

For formularies such as Australia's pharmaceutical benefits scheme (PBS) as well as commercial payers such as those in the United States who are looking at drugs and their value to the public to whom they are responsible, PGx testing allows identification of subpopulations for whom there is an unmet need and greatest benefit [13, 14]. However, little progress has been made on the pharmacoeconomics of the prospective use of genomic biomarkers in the prediction of the benefit-risk ratio for patients. Notwithstanding, there are many examples of genetic variation being significantly associated with ADRs and effective as Dx in clinical practice, such as hepatotoxicity and hypersensitivity reactions [15]. Case studies teach us that genetic variation in the drug target (e.g., receptor) and signal transduction pathway of the majority of drugs accounts for much of the variability in response to medicines [13]. Variation in genes associated with immunological reactions and pathways can also be implicated in drug safety, most notably the MHC/HLA system. One such example is in the use of a PGx test for HLA-B*5701 prior to the administration of abacavir has resulted in the complete mitigation of cases of serious hypersensitivity reaction to the drug. Subjects who are HLA-B*5701 negative almost never develop immunologically-confirmed hypersensitivity reaction upon secondary administration of abacavir, on the other hand, HLA-B*5701 positive subjects (5% of the Caucasian population) have a 70% chance of developing a serious hypersensitivity reaction leading to hospitalization and possibly death if untreated [16].

The FDA and EMEA in addition to other regulatory agencies around the world, have experience with PGx integration into drug development. The FDA has substantial experience with how PGx may be used and there are now several FDA-approved drugs with PGx information in their labeling [5]. This illustrates that there is now a clear expectation that PGx data would be available on safety and efficacy and the FDA has published guidance on this [5]. The FDA has now seen PGx used where variability in response or exposure is observed, where adverse events are a concern, where drug dosage adjustment based on genotype is suggested and where known polymorphism at the target and or signal transduction pathway is evaluated. ADME gene variation involved in the metabolism of molecules has also been seen by the regulators and several molecules approved have ADME genotyping recommendations in the label (aripiprazole and CYP2D6 metabolizer status is an example).

3 The Roadmap to "Pipeline Pharmacogenetics"

3.1 Scientific Rationale

Pharmacogenetics, like any discipline employed for the purpose of improving the way drugs are designed and developed, is first and foremost a science. It is critical that during the course of PGx application this perspective remains the leading prin-

ciple during the selection of methodologies, technologies and analysis procedures. This is particularly true given the exponential growth seen in recent years in scientists' capability to sequence genomes, analyze Big Data and integrate complex phenotypic and medical information into clinically meaningful health management decisions. Still, one may ask—what is the advantage of embarking on the PGx process at early development phases, given limited power considerations associated with the size of these studies (often only a few hundred patients are collectively exposed to an investigational drug leading up to Phase III of its development)? After all, one could argue that postponing the investment would enable focusing efforts on drugs only after demonstrating favorable proof-of-concept (PoC) results and passing the initial safety hurdles. The counter argument lies in the very premise of the concept of "Pipeline PGx", and is well supported by positive, as well as negative, examples: the initial clinical development phases stand to benefit the most from the PGx methodology. PGx-enabled PoC design can maximize efficacy signals and exclude safety outliers so as to shift the overall benefit/risk ratio, resulting in increased probability of technical success early on for the entire program. *Post hoc* attempts to rescue development programs incur costs and waste valuable time depriving patients of effective treatments. History has repeatedly shown that only pre-emptive and systematic application of available scientific understanding of the mode-of-action of drugs and associated pathways can yield pharmaceutical successes that meet regulatory requirements. It is this mind-set and systematic approach that led to the development of a predictive test for abacavir hyper-sensitivity reaction described above [16, 17] or the positioning of prasugrel in a highly competitive landscape against clopidogrel [18, 19]. It is also thanks to this approach and adoption of emerging scientific discoveries that enabled the refocusing of the development of crizotinib from a c-Met-inhibitor to an anaplastic lymphoma kinase (ALK)-inhibitor, and thus formed the target of a co-developed diagnostic for defining patient eligibility [20].

3.2 Sample Collection Strategy

PGx research depends on the collection of DNA samples to generate data. In order to respond to the regulatory authorities' guidelines associated with genetic analysis, most pharmaceutical companies are now devoting resources within their clinical trial programs to enable the collection and storage of DNA samples. These DNA samples provide the pharmaceutical industry with the opportunity to investigate drug response, thereby increasing the likelihood of developing better therapies for patients and enhancing our understanding of the of disease context (e.g. progression and subtype characteristics compounding PGx outcomes) [21]. The collection rates of optional DNA samples, however, remain below the ideal target rate of 90–100 % which appropriately represents the PGx population out of the overall clinical trial ITT (intention to treat) dataset. This variable collection rate may be due to a variety of reasons as listed in Table 1.

Efforts should be made to mandate DNA sample acquisition across all programs where it is determined that DNA collection has a clear rationale and local laws/

Table 1 Common reasons for insufficient DNA sample collection rates in clinical trials and suggested mitigation plans [5, 22, 23]

	Issue	Mitigation plan
1	Insufficient understanding of the informed consent by clinical trial subjects	Ensure following best practices for informed consent writing [24], ensure site staff is knowledgeable and supportive (see 2 below)
2	Lack of support or interest by the site staff	Ensure communication to Principal Investigator clearly states the rationale and medical value of PGx testing in the study. Education program via Investigator Meeting, study newsletters as well as support and accessibility of knowledgeable PGx personnel
		Real-time. Incentivized DNA collection monitoring program Clear lab manual instructions that are easy to follow
		Mandatory DNA collection with clear underlying clinical justification is best practice.
		Incorporation of clear requirements in proficiency of DNA sample collection capabilities and attitudes should be incorporated a priori into site selection procedures
3	Reluctance of CROs to invest efforts in genetic study submission requirements	Select CROs experienced in DNA collection globally Include performance matrix of DNA collection as key elements of service contract Ensure communication to CRO clearly states the rationale and medical value of PGx testing in the study Mandate review by sponsor of country-specific submissions along with up-to-date regulatory guidelines in each recruiting country Establishing routine monitoring procedures for submission and sample collection
4	IRB/EC variation in interpretation of regulations	Clear protocol and ICF language on the purpose and rationale for DNA collection, adjusted to the specific requirements (in terms of detail and format) to each target country and recruiting center
5	Lack of logistical infrastructure	Select central labs with proven capabilities in collection and handling of samples intended for DNA collection (including tumor source) Consider providing refrigerators, centrifuges, dry ice, etc. as needed to ensure quality of samples maintained throughout the custody chain
6	Perception that DNA samples are associates with greater privacy violation risks than the collection of other types of samples during the clinical trial	Dialogue with Key Stakeholders regarding coding practices such that equal standards are applied to DNA and non DNA samples

regulations permit, and ideally from all mid and late phase programs as means for risk mitigation. DNA collection at baseline allows appropriate regulatory utility if and when needed [5]. The benefits of DNA sampling and storage are evident in drug labels, and contribute to internal decision making and regulatory filings [21]. Collecting DNA samples at >90% rate is key to successful and effective translation of findings into improved performance, given that otherwise any such attempt would be significantly compromised by the requirement to conduct new confirmatory prospective studies [21]. The underlying working assumption of PGx, in drug development terms, is valuable *only* when it is delivered in time for project team decision-making. Ultimately, timeliness of results is what facilitates achieving the objectives of each drug development program [14].

A DNA sample collection strategy requires the following key elements:

DNA Sampling Strategy Senior management within the company must provide explicit support that will allow for a clearly defined process to collect DNA samples within clinical trials to address clinical, scientific and regulatory issues in drug development [23]. Ensuring open communications and responsiveness to IRBs, ECs and other Regulatory bodies in the collection process will help to fully utilize the value of PGx research [22]. Funding will also be required in order to create the appropriate infrastructure to not only collect the sample, but to track the collected DNA samples to allow for timely and complete reconciliation (i.e. matching signatures on consent forms with acquired samples at the storage site). An integrated sample management process ensures efficient access to the samples to support the PGx analysis as well as ensures a method to keep the samples secure and private, allow for the tracking of the DNA sample from collection through to genotyping, storage, utility, destruction throughout the chain of custody to support the PGx analysis.

Training Education and training on the value of PGx and why there is the need to achieve optimal DNA collection rates must be provided to both key internal stakeholders (clinical project teams and their operationally focused colleagues) and external collaborators (such as contracted clinical research organizations (CROs) and clinical trial site staff) [14]. A patient's level of understanding of how these samples will be used can be influenced by the level of the investigator's enthusiasm for genetic research.

Informed Consent To be able to use a DNA sample collected in a clinical trial there needs to be a consent form that pre-defines the genomic objective prior to sample acquisition. These objectives can include pre-planned analysis around known factors that are likely to influence the safety, efficacy and/or dosing of the drug [5]. These types of analyses often require access to individual clinical information, particularly in cases of safety investigations. Broader investigations of an open-ended nature can also be considered as long as the sponsor clearly states that intended research will be limited to PGx purposes, i.e. understanding the response profile of the drug. Sponsors wishing to engage in further unspecified broad research which is beyond the scope of PGx would need to separate this research objective from the

PGx objective, placed under strictly voluntary basis, and often commit to anonymizing samples before analysis.

There are some special considerations to take into account when developing the consent form. Regulations around the informed consent vary both globally and locally. To allow for the main study to move forward without any delays, many pharmaceutical companies have created a separate genetic consent form from the main study consent, due to the additional approvals that may be required for collection of genetic samples and PGx research [25]. There are other special considerations that may need to be addressed in the consent form, such as possible ethical implications of the collected data, security and privacy terms of the acquired genetic information and under what circumstances research results might be returned back to the study participants [25].

Sample Collection PGx samples should be collected from all subjects randomized to treatment in all cohorts and in all phases of clinical trials to ensure samples are collected from subjects who have the potential to have a variation in response to the drug [5]. Collection of these samples at the time of enrollment will ensure minimal bias (avoiding lack of representation of DNA samples from subjects who withdrew from the study for any reason) and importantly ensure coverage of sampling from subjects subsequently experiencing ADR during the course of the study. The sample set also needs to be representative of the targeted population for the therapy to cover genetic variation among individuals from different geographic locations [22]. The voluntary and incomplete nature of many exploratory genetic studies conducted in prior years has often raised concerns about potential bias and statistical power, which could compromise the scientific rigor of such studies [5]. There are multiple sample types that can be used for DNA analysis additional to blood (e.g. buccal swabs, hair follicles, etc.) and are particularly relevant to pediatric or other special populations. Furthermore, in oncology studies tumor source DNA and/or circulating tumor cells (CRC) are also required to fully capture the PGx associated variation source that can affect the studied endpoints. When considering DNA samples from sources other than blood a robust quality assurance and quality control programs must be put in place to ensure sufficient yield and DNA quality [14]. This is particularly important when considering tumor source DNA sampling, including aspiration, formalin fixed paraffin-embedded tissue (archived versus fresh), fresh frozen biopsy, etc. and likely to differ from one cancer type to another. In these cases it is beneficial to collect tumor DNA at treatment failure so as to investigate mechanisms of resistance to therapy which are often underlined by the tumor's rescue mutations.

Sample Retention The retention of the DNA sample allows for the opportunity to perform investigations that may occur after the completion of the studies. Samples should be retained for a time period that will permit post marketed analysis should the need arise (e.g., at least 15 years) [5]. Long term sample storage will allow for the investigation of not only observations that emerge during the trial, but also any observations that may occur in subsequent trials and in the first several years after the drug has been on the market. These can be used to investigate external claims

generated by other groups once the drug is marketed, and may facilitate study of additional indications as part of the life cycle management of the product.

3.3 Fit-for-Purpose Genetic Interrogation

Traditionally, PGx studies were performed using a candidate-gene approach, often with genetic variants of the molecular drug target itself, or key polymorphic genes up or downstream in the drug target biological pathway. While candidate-gene hypotheses are statistically powerful, testing discrete genetic drug response hypotheses with a small number of variants, hypothesis-free approaches offer the opportunity for discovering novel genetic markers of drug response and revealing novel biological pathways. These genome-wide methodologies can be performed with custom or commercially available SNP arrays (genome-wide association studies/GWAS), and more recently have incorporated genome-wide sequencing technologies (whole genome sequencing/WGS or whole-genome exome sequencing/WGES). The shift to genome-wide genetic investigations has evolved as a consequence of several factors including lower costs for genotyping or sequencing, better statistical analysis methods and improved design of PGx clinical studies.

Historically, genome-wide association analyses of disease susceptibility have identified common sequence variants that impart modest, 10–20 % increases in disease risk. In contrast, the genetic risk attributed to variants associated with drug response (safety or efficacy) has been much larger (300–2000 %) [26, 27]. One explanation for this large difference in disease vs. drug-response genetic risk ratio could theoretically be attributed to the shorter period of evolutionary time that humans have been exposed to drugs, resulting in decreased selection pressure [28]. Leveraging this interaction of a patient's genome with drug response provides the potential to prescribe the right drug to the right patient (and at the right time for the right cost!). It should be noted that even though PGx science may lead to improvements in drug development, registration and patient health, its implementation has been hampered by the opinion that it might not be cost-effective [29]. However, this argument is becoming less relevant as costs of genotyping technologies drop and as central labs and medical centers increase their investment in genetic testing. Coupled with this is a robust improvement in the technology and breadth of gene tests available in a point-of-care instrumentation format that can provide the clinician with immediately actionable genetic information for personalized prescribing.

3.3.1 Technology of Choice, Genotyping and Sequencing

Candidate gene studies, utilizing either small number of often functionally significant SNPs in a key gene or a few genes (e.g., drug target or critical gene in drug target biological pathway) provide concise answers to specific gene association questions. They are usually employed if there is *a priori* genetic evidence that implicates a particular gene in drug disposition (ADME genes) or drug-response for efficacy/

safety purposes. Targeted gene variant assay panels are widely available from commercial sources and validated for use in diagnostic applications [30, 31]. Candidate gene studies have the advantage of being technically robust and are generally used to confirm a genetic hypothesis derived from a preceding study or reported finding. The original study(ies) is thus referred to as "hypothesis-generating", and often relies on approaches like customized, therapeutically- or disease- focused arrays or GWAS. The results of later confirmatory candidate gene studies often form the basis for development of a genetic companion diagnostic(s) co-development program, temporally synchronized with registration studies for a specific therapeutic.

In contrast, larger customized-array approaches or genome scans are undertaken when little or no genetic information exists, linking the clinical phenotype of interest to specific gene(s). Until recently, whole genome genotyping was usually more expensive than a candidate gene/SNP approach and results were limited to fairly common genetic variants that were selected for coverage across the entire human genome. Recently however, high-density arrays with tagging SNPs capable of assaying genetic variation down to ~1 % minor allele frequency (MAF) have been combined with custom arrays allowing the examination of groups of genetic variants with particular functional significance (e.g. exome arrays, ADME arrays, HLA arrays) [32].

Whole-genome sequencing (WGS) [33, 34] and whole-genome exome-sequencing (WGES) [35–37] costs are also plummeting and these technologies will ultimately replace array-based genotyping approaches in the near future. Advantageously, cheaper WGS and WGES [38] will permit transition away from GWAS-common variants to inclusion of rare genetic variants with potentially greater clinical effects. While accounting for a lower number of patients per specific variant, phylogenetic and coalescence methods are enabling the clustering of evolutionary-related variants into powerful genomic associations [39]. These WGS off-the-shelf products now widely validated for accuracy and coverage, also possess the advantage of condensed order-to-result timelines, since customized array solutions typically require 12–16 weeks for array design and manufacturing. These timelines are often incompatible with clinical development deadlines and force pharmaceutical companies to revert to pre-designed solutions in many cases. In fact, the high cost and complex logistics of obtaining properly consented DNA samples from well-phenotyped clinical trial subjects coupled with the ever decreasing costs of genotyping or sequencing on a genome-wide scale mean that GWAS or WGS/WGES is often cheaper than a candidate gene approach. Thus in practice a large database can be created of genetic variation across the genomes of the entire clinical trial cohort and then sequentially queried *in silico*, starting with a concise candidate gene analysis (hypothesis testing) and ending with a genome-wide screen for genetic variants with large effect (hypothesis-generation) [40, 41].

3.3.2 Statistical Analysis Considerations

The major objective of PGx analysis is to identify genetic marker(s) that can differentiate distinct subgroups of patients in a clinical trial based upon their drug response. Additionally, the pharmaceutical industry is also interested in discovering

genetic variants that are prognostic of a specific disease state or rate of progression of a pathological phenotype. Analytical models for predictive genetic markers include an interaction effect between genotype and treatment while prognostic markers are generally a main effect; where "response" is independent of drug therapy [42].

Early exploratory PGx studies generally analyze many potential genetic variants (candidates) or even scan entire genomes (GWAS, WGS, WES) to identify genetic markers, but small sample size/power, multiple testing, and a high false discovery rate can constrain the ability to discern valid, statistically significant results [43–47]. One key approach to screen out false positive results is to replicate results from the initial exploratory study in a separate clinical trial with similar patients and treatment. Lastly, a prospective, confirmatory study is necessary to test hypotheses related to specific genetic effects and evaluation of the clinical utility of the genetic markers (e.g. specificity, sensitivity, positive predictive value and negative predictive value), establishing the qualifying performance characteristics of the genetic diagnostic (Dx) as a basis for its regulatory approval. Therefore, three separate clinical trials (exploratory, replication, confirmatory) are necessary to go from discovery of a genetic marker to a companion diagnostic, reinforcing the need to start a PGx strategy early in the drug development pipeline.

Study design considerations are important at all steps of the PGx pipeline process. For confirmatory studies, consideration of targeted, enriched or stratified trial designs can be advantageous [48], but are usually only employed when there is an abundance of *a priori* information on a particular genetic marker. Adaptive studies or "gated" approaches permit the analysis of particular genetically defined subgroups when a study fails to meet its primary objective(s), and statistical concerns about multiple testing can be controlled by judicious "alpha-spend" [49]. For exploratory studies, weaker genetic effects can be revealed by using an extreme-phenotype approach that accentuates the differences between subgroups (e.g. super-responders vs. non-response) [50], and variations of this approach may be of particular importance for the study of genetic markers related to serious adverse events (SAEs). Lastly, improvements in the integration of genetic, genomic and clinical information, coupled with newer analytical techniques like Bayesian approaches, multivariate analysis of genetic "features" (SNPs, CNVs, SNVs, etc.) [51, 52] or phylogenetic analysis of sequence data [53], will create new ways to evaluate PGx study data and discover and develop more robust genetic markers of disease and drug-response.

The cost of functional validation can be high if a large number of gene associations emerge from GWAS or sequencing studies, and predefined lists of candidate genes in biological pathways of interest are often chosen for follow-up association studies. Approaches that combine GES with functional genomic bioinformatics filters (e.g. protein folding, gain/loss-of function predictions) or systems biology approaches (genetic, genomic, proteomic, metabolomics, etc.) [54] can also be used to prioritize results for wet-lab functional validation and may uncover novel pathways of biological relevance that are missed in pre-determined analyses.

In conclusion, drug trials of the future will be focused on genomically-targeted patients; identifying those most likely to respond to treatment and least likely to have an adverse event [55–57]. Synergistic effects of high-resolution genomic data (e.g. DNA/RNA sequence), better statistical analysis methods, rapid testing, as well as cheaper genomic analyses will translate into substantial savings in drug development cost and greater patient benefit.

3.4 Integrated Execution Methodology

Opportunities for PGx and the value to the portfolio exist throughout the development process from preclinical through Marketing/Pharmacovigilence, as long as PGx is in lock step with discovery and clinical development milestones. For this value to be realized, PGx objectives must be integrated into study protocols from early drafting to ensure that the proper support framework and budget are in place for sample collection, data management, and statistical analysis. In addition, experienced PGx personnel should be fully integrated into the clinical development teams from their inception point. The PGx team should be led by a scientist and consist of contract and vendor manager, genomic data manager, statistician, bioinformatician, and PGx project manager.

3.5 Communicating with Stakeholders

Managing the exchange of information and expectations across and outside the organization is challenging, though essential, for a successful drug development program. The internal and external stakeholders for PGx information are similar to other elements of the Clinical program, though some specific considerations are noteworthy for a PGx program.

Internal Stakeholders

Drug Discovery teams:
Disease genetics can be critically important in target and lead identification and validation, making PGx involvement at the earliest stages of discovery highly valuable.

Clinical trial design teams:
Integrating clinical objectives (primary, secondary, exploratory, gated) in clinical studies is the key to generating both retrospective, as well as prospective, actionable genomics results, tailored specifically for the enrolled population.

Clinical operations teams:
Once PGx is built into the clinical program, managing sample collection and clinical data availability is necessary.

Drug program/management teams:
Overarching program teams defining the overall strategy for the compound and evaluating novel indication or combination strategies for the compound, need to

be informed of the PGx progress and results, especially if and when unfavorable safety and efficacy results emerge in a study. If an integrated, prospective approach is taken, PGx information can be used to save some programs in light of results that would initially seem to kill a program.

Senior management (technical and non-technical):
Decisions of funding and ultimately the fate of programs facing unfavorable results are generally in the hands of senior managers that may not have specific and technical PGx background. Keeping management informed of the PGx strategy and value proposition, as well as current results is essential.

External Stakeholders
Regulatory Agencies:
As with much of the work companies plan and execute to develop drugs, communicating PGx plans and results to regulatory agencies in a timely manner is critical, especially at key clinical milestones. Agencies endorse the use of PGx information to increase the understanding of patient safety and drug efficacy as part of the benefit-risk assessment [58]. Furthermore, several communication routes are possible to convey PGx related information and should be chosen as appropriate, including for instance in the FDA the voluntary exploratory data submission (VXDS) route (non-trial specific), the "conventional" submission route to CDER, and co-development route to CDER and CDRH simultaneously.

Academic collaborators:
Trial recruitment rate is often better when key opinion leaders in the relevant therapeutic areas are involved in research and development of drugs. Including participation of academic collaborators in the PGx aspects of projects can often provide added benefit. This is also key for smooth introduction into the clinic and correlates well with market adoption at commercialization.

Payers:
Optimizing the health outcomes of patients is the primary goal of payers. Understanding payer's willingness and overall market drivers for drugs with PGx opportunities and label information will aid in developing a realistic value proposition, especially with companion diagnostic opportunities.

Physicians:
Beyond the physician's involvement in clinical trials, increasing the physician-wide knowledge of PGx and drug safety and efficacy will ultimately lead to better adoption by patients.

Patients:
Patients demand personalized approaches to many projects and services, and have increased willingness to provide genetic information when participating in clinical trials. Reaching out to patients or advocacy groups with regards to the opportunities to improve health and wellness through PGx is essentials. Recently patient advocacy groups have shown to be instrumental in targeted therapeutic approaches to drug development, for instance in the case of Cystic Fibrosis and Vertex's Kalydeco.

4 Pipeline Pharmacogenetic: Practical Application

For PGx to be successful, the objectives, tasks, and supporting roles (internally and externally) must be managed with a systematic methodology. Employing the established framework of formal Program and Project Management will maximize the delivered value of PGx. Since new molecular entities and drug candidates are considered *Program-level* effort due to the long timeframe (> 10–15 years from candidate selection to end of patent protection, plus possible product line extension), the corresponding PGx effort integrated in the development of these assets should be managed as a Program. The key deliverable emerging from a properly managed PGx Program is a PGx Strategy that is fully integrated and aligned with the asset development program. In a similar manner, individual preclinical and clinical studies that support assets are considered projects since they are a "temporary endeavor undertaken to create a unique product, service or result" [59], so the corresponding PGx experiments and studies should be managed as projects that are arranged and executed to secure the goals set within the PGx Strategy.

4.1 PGx Program Stages

The ideal PGx program would start very early in the asset life cycle, possibly pre-candidate selection or even at or as part of biological target identification. However, even mature assets with established clinical programs in Phase 1–3, possibly even approved and marketed assets, can initiate a PGx program. There are 3 key stages in the life cycle of a PGx Program illustrated in Table 2 [14].

Confirm When PGx is first considered for a drug candidate, the PGx team should be gathering and evaluating information related to disease biology, existing genomic factors for the biological target and potential patient populations, competitive landscape, early safety signals, available information on ADME, and other information useful to start formulating a PGx strategy. This early exploratory program stage results in the confirmation that there is indeed a PGx opportunity for a particular asset.

Integrate The chief purpose of this program phase is to establish the initial integrated PGx strategy, and to convey the value that PGx will bring to the particular asset and overall portfolio. It is recommended that this guiding information be recorded in the PGx Strategy and Value Proposition document (SVP) at this phase. The SVP is an overarching, "living" document that would serve as a reference point for all tactical decisions related individual PGx projects (Sect. 3.5.2). Stakeholders and funding sources (e.g. clinical teams, senior management) should be in agreement with the PGx strategy at this point.

Implement and Refine Once the PGx Strategy is established, this final Program phase is essentially the PGx program at "steady state" and is the longest phase,

Table 2 Pipeline Pharmacogenetics (PGx) Program Methodology

I. Confirm	II. Integrate	III. Implement and refine
Purpose:	*Purpose:*	*Purpose:*
Understand molecule, gather information and confirm PGx opportunity	Integrate with development team, create initial PGx strategy, identify value proposition	Implement PGx strategy, execute PGx experimental projects and deliver refined PGx strategy
Activities:	*Activities:*	*Activities:*
Molecule investigation via review of: - Preclinical data - Intended therapy - Target and pathway - External literature - Portfolio priority - Existing Clinical data, if available	Engage clinical team via: - Detailed molecule investigation - Review safety signals - Understand label, differentiation goals, development plan	Operationalize PGx via: - Protocol development, regulatory planning, and trial execution - Experimental project execution - Results interpretation - Strategy refinement
Key deliverable:	*Key deliverable:*	*Key deliverables:*
PGx molecule assessment	PGx strategy and value proposition	Experimental data and interpretation PGx strategy refinement

where individual projects are executed in alignment with the strategy. New information is gathered from external sources and results from implemented PGx projects, and the PGx strategy and corresponding SVP document are updated and refined to adapt to the changing situation of the asset.

4.2 PGx Project Stages

Once the PGx strategy is developed and clinical integration points are established, PGx projects should be implemented within the program by using the following 5 stages illustrated in Table 3 [14].

Scope A considerable part of "scoping" a project is in the gathering of specific clinical trial information from which genomic samples will be used along with the available clinical data. If the clinical team incorporated PGx objectives in the protocol prospectively and clinical samples and data were collected in preparation for PGx analysis, then this stage will largely be focused determining specific genomic assay platforms, vendor selection, and cost estimates. Also during this stage, the PGx lead should have specific engagements with the clinical team and funding sponsors (e.g. senior management) to reacquaint internal stakeholders to the purpose of the project and secure funding support. The final objective of this stage is to clearly delineate and document the objectives and boundaries of the project. This is critical to prevent "project creep" without deliberate and controlled scope revision,

Table 3 Pipeline Pharmacogenetics (PGx) Project Methodology

I. Scope	II. Plan	III. Execute	IV. Interpret	V. Close
Purpose:	*Purpose:*	*Purpose:*	*Purpose:*	*Purpose:*
Determine if a project will contribute to the PGx strategy, is feasible, and will be timely	Develop the project plan, identify deliverables, acquire resources, and create work breakdown and schedule	Execute the defined work to meet the project deliverables	Interpret the results of execution and recommend necessary next steps	Actively close the project, archive records, and perform post-project assessment
Activities:	*Activities:*	*Activities:*	*Activities:*	*Activities:*
Investigate: - Samples - Phenotype - Genotype - Statistical power - Technical feasibility - Strategy alignment	- Select deliverables - Create Project plan - Select vendor and technology - Work breakdown - Create schedule	- Genotyping - Genotyping data delivery - Statistical and power analyses	Statistical analyses results interpretation	Perform document quality checks, collate project archive, and represent findings in updated PGx strategy
Key deliverables:	*Key deliverables:*	*Key deliverables:*	*Key deliverables:*	*Key deliverables:*
Scope summary Project charter	Deliverables list Genetic variant list Genotyping contract PGx statistical analyses plan Project schedule	Genetic data and QA results Statistical requirements, output and report	PGx results interpretation and recommendation	Project archive binder Refined PGx strategy and value proposition

which is inevitable when clinical results emerge, organization priorities shift, and new genomic techniques/approaches are considered.

Plan Once the scope of the PGx project is finalized and approved, the planning of the project is initiated. The detailed project schedule is established and the overall operations and expectations of the project, including expected activities, deliverables and special considerations are documented in a Project Charter.

Execute Most of the expected activities defined during planning occur during the execute stage of the PGx project, usually starting with the planned genomic assays, including sample shipment and vendor management (if applicable). Other activities may include genomic data QC, development of statistical analysis plan and defining the expected table/lists/figures, genomic data transmission and merging with clinical data, and performing statistical analysis.

Interpret After the statistical analyses evaluating genetic associations with clinical responses/outcomes have been completed, the interpretation of the data and development of a recommended next step occurs. This important stage is led by the PGx

Scientist in consultation with the PGx statistician and clinician/clinical team, where necessary. The output of this stage is usually the results interpretation and recommendation document or report that can be summarized and incorporated into regulatory submission documents, manuscripts, etc.

Close In the final stage of the project, all PGx related documentation is stored and archived to retain the necessary information for regulatory review and future projects as part of the same program or for other programs with similar strategy and implementation.

5 Specific Examples in Early-Development

5.1 OPRM1 PGx and Alcohol Dependence

Pharmacotherapy of alcohol dependence shows widely divergent responses both within and between patients, and part of this variability can be attributed to the underlying genotype. Recently, treatment response to the opioid receptor antagonist naltrexone was shown to be predicted by a genetic variant of the OPRM1 gene (rs1799971) [60]. In a recent study, the effect of two genetic variants in OPRM1 and a variable-nucleotide tandem repeat (VNTR) in the dopamine receptor gene (DRD4) were evaluated for association with the clinical efficacy of a novel opioid receptor antagonist for the treatment of alcohol dependence [61]. Asp-carriers of the OPRM1/rs1799971 genetic variant did not demonstrate an enhanced response to LY2196044 treatment when evaluated by changes in % heavy drinking days (HDD), % days abstinent, or drinks per day. Surprisingly, however, placebo-treated Asp-carriers demonstrated a blunted response to standard medical management versus Asp-non-carriers by all efficacy measures. This Asp-carrier dependent "placebo-effect" reached statistical significance for change in % days abstinent and drinks per day ($p=0.0202$ and $p=0.0093$, respectively) but not change in % HDD ($p=0.1261$). Val-carriers of the OPRM1/rs1799972 variant treated with LY2196044 consistently had greater reduction in % HDD, % days abstinent, and drinks per day, but none of these reached statistical significance ($p=0.0653$, 0.8895 and 0.1073. LY2196044-treated patients who were DRD4-VNTR L-carriers had greater reductions in % HDD ($p=0.0565$), increased % days abstinent ($p=0.0496$), and reduced drinks per day ($p=0.0069$) than placebo-treated L-carriers.

In this study, Asp-carriers did not show a greater response to LY2196044 treatment, but instead had a blunted response to medical management in the placebo group. The difference between this result and earlier reports may be due to the differences in pharmacological profiles between LY2196044 and naltrexone, trial designs, definition of clinical endpoints and/or response, or unknown phenotypic differences within this trial population. The DRD4 L-carriers comprised >39% of the trial participants and showed statistically significantly superior treatment response. DRD4 L-carriers have demonstrated better response to other treatments for

alcohol consumption including olanzapine [62] and naltrexone [63]. Thus, DRD4-L may represent a common, robust genetic marker of opioid receptor antagonist response and form the basis for a potential tailored drug development program and companion diagnostic.

5.2 Oncology and Rare Diseases/Early Phase

One of the most vibrant and successful areas for implementation of PGx has been oncology. Recent years have seen development of novel therapeutics that is almost exclusively a "targeted therapeutic" approach, requiring a co-developed test to identify the target responder population. The greatest successes in this realm over the last couple of years encompass the ALK-inhibitor, crizotinib, and the B-Raf inhibitor, vemurafenib. Already at early phase I studies was a beneficial effect demonstrated in marker-positive carriers, which formed the basis for development decisions and study design for each of these molecules. Competitors are now developing second-generation BRAF and ALK inhibitors, benchmarked by the first-to-market compounds, both in terms of efficacy, as well as in terms of diagnostics and combination therapy.

Another immediate application for PGx early on relates to the growing clinical development field of rare diseases. Increasing in-depth characterization of the molecular biology of inherited disorders, fueled by financial incentives in the form of the Orphan Drug Act and expedited regulatory review processes, such as Fast Track and the Breakthrough Therapy designation, have led many biopharmaceutical companies to focus efforts on these ailments. Some of the successes in this field have revolutionized the care and life-expectancy of subjects with diseases such as Fabry disease (Fabrazyme), Pompe disease (Myozyme) and Cystic Fibrosis (Kalydeco) [64]. In these cases, the development is targeted for carriers of specific mutations and may employ comprehensive genetic and molecular screening already at early phases, followed by limited to no requirement for late stage registration studies prior to marketing approval.

6 Late Stage Drug Development and Pharmacogenetically-Enabled Clinical Trials: Rx/Dx co-Development

A drug development plan accompanied by pre-emptive Pipeline PGx approach from the get-go should culminate in late, Phase III clinical trials with a focused, well designed PGx component. It is not to claim that all drugs should be guided by a PGx designation, rather that by the time a drug is tested for registration purposes, the PGx characteristics of its efficacy and safety profile should be embedded into the program. The translation of this statement could mean a range of possibilities, depending on the specific drug and indication, starting with screening subjects for

eligibility based on carrier status of a particular genetic variant (i.e. the genetic predictor will become a required biomarker for prescription purposes), through to exploratory study of potential findings as no large PGx effects are anticipated based on pre-clinical and early development studies. In the latter case, exploratory analyses (and integral sample collection) are pursued to account for unexpected adverse drug reaction and other unexpected findings, such as high PK variability. The recently published draft guidance from FDA on enrichment strategies in clinical trials is the agency's response to recent development programs that employed genetic and other biomarkers in order to demonstrate favorable and safe benefit-risk balance [48]. One of the fields that have seen most innovation and creativity in this aspect has been Alzheimer's disease (AD) clinical research. The first such late-phase trial employed genotype of the apolipoprotein E (APOE) epsilon 4 (E4) gene as stratification biomarker toward development of rosiglitazone for the indication of mild-to-moderate AD treatment. The design was based on a prior Phase II trial that showed efficacy in an exploratory PGx analysis in APOE E4 non-carriers. The main Phase III study failed to reach its co-primary endpoints. Unfortunately, the result does not necessarily reflect lack of efficacy in this target indication as a high proportion of the study participants were of Asian ancestry, unknown at the time to possess a genetic signature that is different than that possessed by Caucasians and other ancestries. To this end, the study was likely underpowered to detect the clinical effect. It did indicate potential efficacy in the low dose arm in APOE E4 non-carriers.

Another set of studies employed APOE E4 carrier status as a patient selection criterion into clinical trials testing the efficacy of bapinuzumab, a humanized monoclonal antibody targeted against extra-cellular amyloid plaques, for the treatment of mild-to-moderate AD. The biomarker was considered to be predictive of drug response based on exploratory analyses of Phase II data, which did not reach statistical significance for its primary endpoint. As a result, treatment response in patients with the APOE E4 genotype versus patients without the APOE E4 genotype, was assessed in two phase 3, multicenter, randomized, double-blind, placebo-controlled studies, which were completed in April and June 2012, each with > 1,100 participants. The initial plan included two active doses in each trial, with the higher dose discontinued in the two APOE E4 carrier studies due to increased risk of amyloid-related imaging abnormalities (ARIA). Neither one of these studies reached statistical significance for clinical endpoints.

It is, however, by now generally accepted by field experts that treating AD at the mild-to-moderate clinical stages is simply too late, as the overt cell death and overall brain damage accumulated exceeds the potential for recovery. Given that neurons do not regenerate, it is unlikely that disease could be reversed once it has passed a critical severity threshold. Instead, efforts are now invested in preserving neuronal capacity at early disease stages (terms Mild Cognitive Impairment, MCI) or, better yet, to delay the onset of first symptoms and possibly prevent AD altogether. However, the feasibility of conducting disease prevention studies in this highly prevalent, yet highly heterogeneous disease in terms of age of onset, progression and clinical course, is very low. It is therefore necessary to employ an enrichment strategy that can pinpoint individuals at high-risk of developing the first symptoms within a short time frame of several years. Furthermore, it is critical to demonstrate

that the potential benefit (i.e. delay of onset) outweighs the risks (adverse events) in a cognitively normal elderly population. Thus, the clinical study design should randomize high-risk individuals into active versus placebo treatment, while the low-risk individuals (expected to live several years before potentially converting their risk status to the high level) should be administered placebo only, in a blinded fashion. This scheme allows for full evaluation of the treatment effects, parallel to qualification of the biomarker in a prospective, unbiased manner.

Other therapeutic areas are employing PGx at the registration phase for various purposes. One important goal is to ensure characterization of already-known biomarkers in the context of novel investigational drugs since, for the first time in the development process, large populations of patients are being exposed to these compounds. To this end, the FDA publishes a list of Pharmacogenomic Biomarkers in Drug Labels mentioned also above. Some, but not all, of these labels include specific actions to be taken based on genetic information, and the scope of biomarker type ranges between genetic sequence variation to expression changes and others. For those genes with known functional relevance to protein activity or/and to clinical outcomes, regulators require and/or encourage developers to evaluate them in the course of clinical development of investigational drugs.

7 Pipeline Pharmacogenetics: Summary

7.1 Barriers

The use of PGx is now fairly common within the pharmaceutical industry. Therefore it is not unreasonable to expect the delivery of tailored therapeutics across many disease areas. However, while PGx has had a dramatic effect on new personalized medicines for oncology, most of the other therapeutic areas seem to be lagging behind. One reason is the lack of organized, therapy-wide PGx strategies for assets at all stages of drug development carried out by skilled PGx scientists and project managers using a comprehensive Pipeline PGx methodology. As described in the sections and examples above, a valuable R&D PGx strategy starts with DNA collections from every subject in every clinical trial and integrates well-designed PGx scientific hypotheses into clinical study protocols. Delivery of time-driven PGx results permits R&D leaders to make key decisions and develop safe and effective tailored medicines.

Unfortunately, many barriers exist to successful implementation of the Pipeline PGx approach within the pharmaceutical industry. First, many argue that statistical significance of PGx effects are impossible to attain in phase 1 or 2 studies. Additionally, some contend that the size of drug-response genetic effects are too small and current studies will be unable to detect them. Both of these opinions are based on a confused understanding of the difference between disease genetics and PGx. There are many examples of very large genetic effects on both efficacy and AE's. In addition, specific genetic variants effects on disease are often quite distinct from

those on drug response. Secondly, anecdotal organizational "opinions" can hinder the implementation of PGx. Many clinical project teams erroneously believe that collecting DNA samples during the course of a clinical trial will impede recruitment, but this has consistently been shown to not be true. Thirdly, many are concerned on how various global drug regulatory agencies will interpret PGx data, and the belief that PGx results may lead to label restrictions and a restricted commercial potential. In fact, regulators have published guidelines on how PGx approaches (therapeutic coupled with a companion diagnostic) can lead to faster regulatory approval, focused labels and safer, more efficacious treatments, personalized for specific patient subgroups.

7.2 Outlook and Recommendations

The application of PGx tools, technologies and strategies to understanding the genetic contribution to pathophysiology and therapeutic response has been successful, and key stakeholders (patients, physicians, regulators, payers) have recognized these achievements. Recent progress in understanding the science of the genome, technological developments and bioinformatic/analytical approaches demonstrate that we can identify genetic markers that contribute to the safe and efficacious use of therapeutics. The evolving regulatory and business climate is placing greater value on increasing specificity and certainty around therapeutic choice.

However, the high attrition rates and reduced productivity of the pharma industry R&D is unsustainable and new strategies for tailoring medicines are needed. Currently, pharmaceutical companies are rarely, and/or inefficiently, leveraging the value inherent in the science of PGx to assist with critical decision making during drug development. One of the reasons is the lack of a systematic approach to incorporate PGx into the standard drug development process. This chapter has described a coherent Pipeline PGx methodology, described the tactical elements of this method, and provided successful examples of its application to drug development. In addition, some of the organizational and conceptual barriers that exist within and outside the pharmaceutical industry have been described. Therefore we recommend routine implementation of the PGx methodology throughout the drug development continuum that will deliver safer, efficacious and valuable tailored therapies for the benefit of patients, healthcare providers, payers, and the pharmaceutical industry.

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