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Genetics, drug discovery and clinical developments

Pharmacogenomic strategies in drug safety☆

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Drug safety is a priority for drug developers and regulatory agencies. Pharmacogenomics is a powerful tool that can be used to manage clinical risks as well as resolve the mechanistic basis of adverse drug events. Advances in the science of drug safety, increased commitment to pharmacogenomics by drug companies, and enhanced regulatory review infrastructure at the U.S. FDA have helped to advance the application of safety pharmacogenomics in drug development and public health decision-making. This review highlights some successes in discovery and translation of pharmacogenomic biomarkers for adverse drug events and outlines future strategies to optimize the development and clinical application of pharmacogenomic information.

Introduction

Adverse drug experiences (ADEs) manifest in a range of events from common, pharmacologically anticipated toxicities to therapeutic failures to rare, severe idiosyncratic drug reactions. Drug safety is a top priority for drug developers and regulatory agencies because toxicological and clinical safety issues halt the development of approximately one in three drugs [1]. Although some ADEs can be predicted from experimental models and managed by careful patient selection or dose modification, novel strategies to mitigate and manage emergent safety issues are needed to foster the development of valuable drugs.

Pharmacogenomics is a powerful tool that can be used to manage clinical risks and resolve the mechanistic basis of ADEs. Historically, the limited detection of ADEs in pre-approval studies, poorly defined safety phenotypes and prediction methods, ambiguous case definitions, lack of stored biospecimens, and technological limitations hindered the ability to characterize the genetic underpinnings of drug toxicities. However, the landscape of drug safety pharmacogenomics is evolving. Public–private partnerships, consortia development, large-scale biobanking projects, and the advent of high-throughput genotyping/sequencing technologies are creating opportunities to discover robust, highly predictive biomarkers for adverse drug treatment outcomes. In addition, increased commitment to pharmacogenomics by drug companies and enhanced regulatory review infrastructure at the U.S. FDA have helped to advance the application of safety pharmacogenomics in drug development and public health decision-making [2]. This review highlights some successes in discovery and translation of pharmacogenomic biomarkers for ADEs, and outlines possible future strategies to optimize the development and clinical application of pharmacogenomic information.

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A pharmacogenomic perspective on drug safety: shifting probabilities

Drug safety issues are generally managed using three non-mutually exclusive strategies (Box 1): (1) monitoring-based intervention, (2) careful patient selection, and (3) risk communication. Drugs that have measurable, chronic toxicities tend to be manageable. For instance, periodic monitoring for the appearance of known metabolic adverse events during antiretroviral or antipsychotic drug therapy allows prescribers to switch drugs, adjust doses, or start supportive therapies (e.g., lipid-lowering therapy). Monitoring liver function test results for drugs that may cause hepatic injury is a common risk minimization strategy. Unfortunately, some toxicities are not amenable to clinical monitoring. In these cases, drug use may be restricted to the patient populations with the greatest benefit/risk balance. As such, numerous drug labels bear warnings for populations in which ADEs occur more frequently, or focus on selecting patients that are most likely to benefit. When the at-risk populations cannot be defined and the mechanism is unknown, risk management may focus on increasing prescriber and consumer awareness so as to influence prescribing or monitoring patterns. Pharmacogenomic strategies could have significant value in shifting unpredictable, mechanistically unclear events to predictable, manageable risks, provided the drug has a clear value.

Box 1. Clinical management strategies for selected ADEs

Monitor biomarkers and therapeutically intervene (e.g., additional drug, dose modification, drug discontinuation) as needed

- *Protease inhibitors*: hyperglycemia, metabolic disturbances and fat redistribution, atherosclerotic cardiovascular disease (monitor metabolic profile)
- *Atypical antipsychotics*: glucose and lipid abnormalities, weight gain (monitor metabolic profile)
- *Anthracyclines*: cardiotoxicity (monitor cumulative dose)

Statins: myopathic syndromes (monitor patient symptoms and creatine kinase)

Exclude at-risk patients from treatment

- *Dronedarone*: death (avoid in heart failure)
- *TNFα antagonists*: heart failure (avoid in heart failure)
- *Contraceptives*: thrombosis (avoid in smokers >35 years old)
- *Droperidol*: QT prolongation (avoid in elderly, alcoholics, patients with other risk factors)

Increase patient and prescriber awareness of risk

- *Rosiglitazone, celecoxib, rofecoxib*[*]: cardiovascular events
- *Cabergoline, pergolide*[*]: valvulopathy
- *Cisapride*[*], *terfenadine*[*]: ventricular arrhythmias

[*] Withdrawn from U.S. market

Pharmacokinetics, pharmacodynamics, and idiosyncrasy

Pharmacokinetic ADEs

The risk profile of drugs that have steep exposure-safety relationships hinges largely on pharmacokinetic variability. Toxicities that are sensitive to disturbances in drug metabolism, mainly because of drug interactions, account for many of the market withdrawals seen in recent decades. Terfenadine, mibefradil, astemizole, and cisapride all were found to have exposure-related toxicities that, when co-administered with enzyme-inhibiting drugs, became apparent in the post-approval setting. Given this history, many promising compounds may never be developed if subject to extensive metabolism by polymorphic enzymes. Therefore, considering the potential impact of polymorphic drug metabolism is crucial to maximizing successful development of potentially promising compounds.

Typically, drug dosages will be modified if significant pharmacokinetic interactions are observed. However, extending the logic of metabolic drug interactions to polymorphic metabolism and transport has not been a widely adopted concept. At present, thioridazine represents one of the only drugs with a contraindication for use in a genetically defined subpopulation (CYP2D6 poor metabolizers) because of the QT-prolongation risk at high exposures. Isoniazid (NAT2 substrate), 6-mercaptopurine (TPMT substrate), and irinotecan (UGT1A1 substrate) have more tolerable risk–benefit profiles, and thus bear warnings for use in slow or poor metabolizers of the respective enzymes in their product labels. Hybrid approaches have been employed more recently. For instance, genotyping is recommended for tetrabenazine, but only when prescribers intend to go above a certain dose threshold. These examples illustrate how drugs may still be successfully developed in light of exposure-related toxicities, so long as the appropriate dosing strategy can be identified.

Prodrugs are often biotransformed to pharmacologically active metabolites by polymorphic enzymes, and thus have the potential for either excessive exposure to the active metabolite(s) or loss of efficacy due to genetic variation in metabolism. For example, codeine is activated to morphine by CYP2D6. Individuals with multiple copies of the active CYP2D6 gene may exhibit high exposures to morphine [3,4]. In fact, opioid toxicities have been reported in ultrarapid metabolizing adults, and in infants breastfeeding from ultrarapid metabolizing mothers [5,6]. At the other end of the spectrum, poor metabolizers of certain enzymes may not be able to generate the active moiety from the prodrug. Clopidogrel, which is activated in part by CYP2C19, and tamoxifen, which is activated by CYP2D6, are two drugs where active metabolite exposures are substantially lower in the poor metabolizers [7–10]. Diminished efficacy resulting from lower active metabolite exposures in these cases is proble-

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matic because these drugs are used to prevent morbid or mortal outcomes (i.e., myocardial infarction, cancer).

Pharmacodynamic ADEs

Genetic variation in drug targets and their signaling pathways can contribute to toxicities extending from the pharmacologic action of the drug. However, few such examples exist; the majority of pharmacodynamic gene variants influence therapeutic drug response. One of the most notable and widely studied examples of pharmacodynamic gene effects on drug sensitivity has been related to the anticoagulant warfarin. The influence of genetic variation in the drug target, VKORC1, has been widely replicated as a marker of stable dose requirements, as has the major drug metabolizing enzyme, CYP2C9 [11]. Intrinsically 'sensitive' patients require much lower doses to achieve therapeutic anticoagulation. Conversely, patients with 'insensitive' genotypes tend to require higher doses and are at risk for under-anticoagulation. The availability of a clinical response measure (INR) affords a means to target dosing to a pharmacodynamic 'sweet spot' that has proven to balance bleeding and thromboembolic risks [12]. Along with INR monitoring, knowledge of VKORC1 and CYP2C9 genotype information could add value in tailoring doses or the aggressiveness of dose adjustment, particularly in the early initiation period where the most INR fluctuation and bleeding are observed [13–15]. The joint consideration of clinical and genetic variables is now reflected in the revised warfarin drug label.

Signaling proteins in a drug's pharmacologic pathway can also have large effects on treatment response. Retrospective analyses from multiple clinical trials of anti-EGFR therapy in metastatic colorectal cancer patients revealed that activating mutations in the tumor KRAS gene were associated with lack of anti-tumor effect of the monoclonal antibodies, cetuximab and panitumumab [16]. This diminished efficacy, therefore, skews the risk–benefit profile toward toxicity without benefit. Thus, it has become a standard practice to test patients' tumors for KRAS mutations before initiating anti-EGFR monoclonal antibodies.

Genetic factors that modify a disease process also may compound drug effects on the same phenotype. Factor 5 Leiden (FVL) is widely recognized as genetic risk factor for thrombotic events. Several studies have demonstrated that patients with FVL who are taking oral contraceptives or estrogens have a 13- to 15-fold higher risk for thrombosis than non-carriers [17]. This relative risk approximates or exceeds the risk associated with age and smoking status, which are commonly considered in clinical practice.

Idiosyncratic ADEs

Idiosyncratic drug reactions are, by definition, mechanistically unclear and not predictable. Severe reactions such as Stevens-Johnson Syndrome (SJS) or fulminant hepatotoxicity tend to be rare, but can be fatal. The rarity of such events makes them difficult to detect in pre-approval clinical development programs. As such, the pharmacogenetic relationships are usually defined in the post-approval setting and rely on small studies without replication. Also, in the absence of a clear mechanism, the research approach tends to be less hypothesis-driven, employing genome-wide association strategies [18].

The aforementioned limitations do not prevent the ability to discover potentially useful markers for rare, idiosyncratic ADEs. Several robust associations have been reported that establish the feasibility of GWAS or HLA-typing for rare events, including SLCO1B1 as a marker for simvastatin myopathy [19], HLA-DQA1*0102 for lumiracoxib hepatotoxicity [20], HLA-B*5801 for allopurinol skin reactions [21], and HLA-DRB5*0201 for clozapine agranulocytosis [22], to name a few. To illustrate, severe skin reactions, sometimes resulting in death, are rare having been reported in approximately 1–6 per 10,000 patients treated with carbamazepine. Investigators in China collected genetic material from carbamazepine-treated patients with cutaneous skin reactions (60 with SJS/TEN, 31 with other skin reactions) and tolerant controls over a seven-year period. HLA-typing revealed that the HLA-B*1502 allele, and other alleles in the neighboring region, were significantly overrepresented in cases (98% of cases and 4.2% of controls; odds ratio 1357, $p = 2 \times 10^{-41}$) [23]. Amassing an adequate – not necessarily large – caseload typically requires collaborative efforts and time, but based on these examples, is not an impossible feat.

Common adverse reactions can be interrogated using more traditional hypothesis testing and validation strategies. Abacavir hypersensitivity reaction, a syndrome consisting of fever, rash, and gastrointestinal complaints, occurs in approximately 5–8% of Caucasian HIV patients treated with abacavir [24,25]. This event was detected in pre-approval trials, and the initial drug label included a Boxed Warning to this effect. Following approval, several genetic association studies, including a GWAS, found that HLA-B*5701 was a significant risk factor for this reaction [26]. The utility of testing was subsequently confirmed in a prospective trial. For patients randomized to a HLA-B*5701 testing strategy, as compared to the non-tested usual care strategy, the incidence of clinically diagnosed (and skin patch testing confirmed) abacavir hypersensitivity was significantly reduced (7.8% vs. 3.4% for clinically diagnosed, 2.7% vs. 0% for immunologically confirmed) [24]. Because this event was more common, it was feasible to conduct a controlled trial to establish utility, substantiating previous findings from retrospective studies.

Translational considerations

A major factor hindering research and development of pharmacogenomic biomarkers of clinical safety is the relative paucity of available cases. Most of the pharmacogenomic

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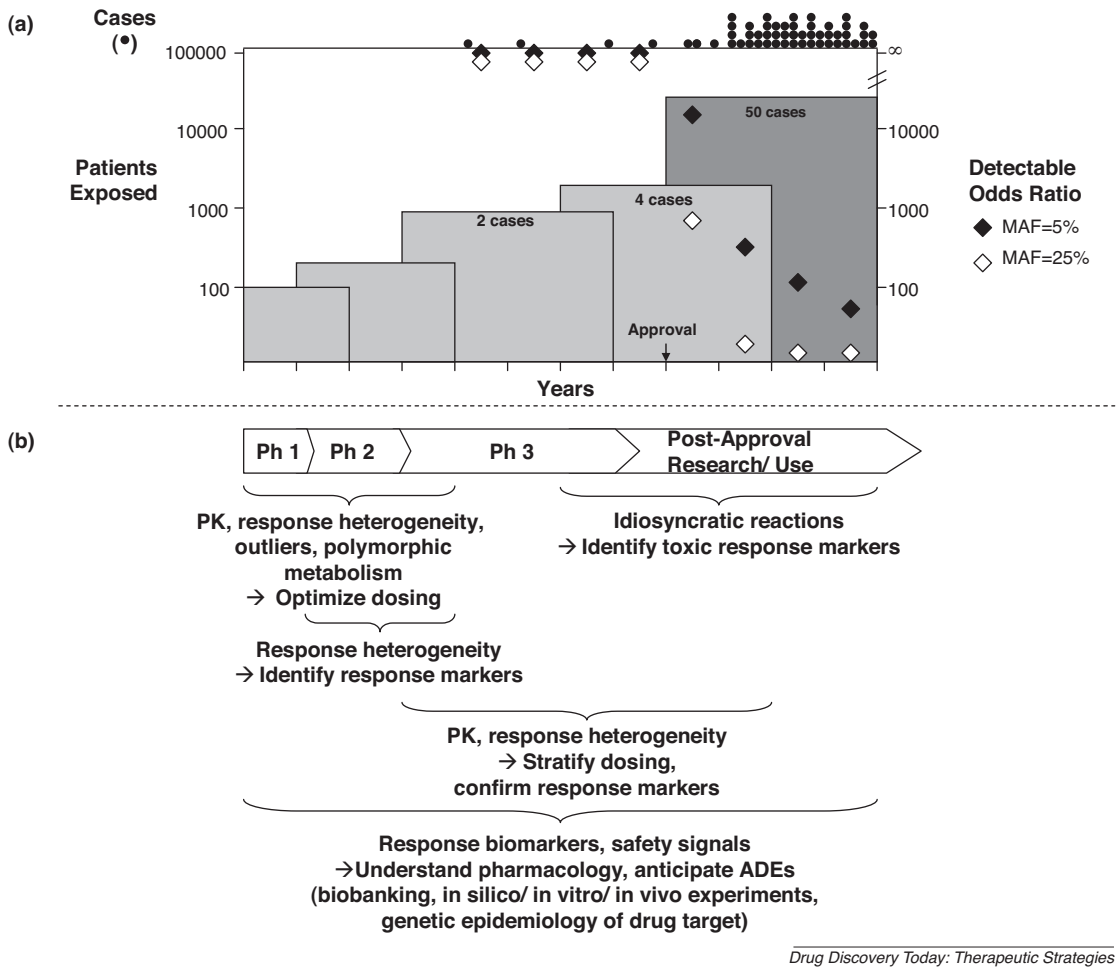

Figure 1. Pharmacogenomic activities in drug development and utilization. Panel A. Patient exposures to a new molecular entity to treat a mortal disease over time in a drug development program and following approval are depicted. As time goes on, the power to detect predictive biomarkers with large effects in genome-wide association studies increases substantially (denoted by diamonds; power calculations for each year assume cumulative caseload at 1/1000 per year incidence, recessive effect, $p < 5 \times 10^{-7}$, and 10 controls per case). Panel B. Pharmacogenomic activities over a drug's lifecycle are depicted. Drug developers can conduct pharmacogenomic studies triggered by pharmacokinetic or response heterogeneity as sufficient numbers of serious adverse event cases accumulate to conduct meaningful genome-wide association studies. The results can be used to tailor dosing and enrich trials with responders so as to optimize the risk–benefit ratio prior to approval. Biobanking efforts throughout the drug's lifecycle can then enable biomarker discovery efforts for rarer adverse events.

biomarkers to date have had very large effects on ADE risk. The examples cited in the previous section, most of which had odds ratios exceeding 100, illustrate that large effects can be detectable even with relatively few cases. As shown in Fig. 1, with 50 cases, the detectable odds ratio is approximately 100 for a less common allele (5%; recessive effect), and approximately 20 for more common alleles (25%; recessive effect). If the infrastructure is in place to capture incident cases in real-time, the power to conduct genetic association studies for rare ADEs will be significantly enhanced.

In addition to large effects, safety biomarkers should have adequate performance characteristics (i.e., predictive value, sensitivity, and specificity) to effectively discriminate risk for potential events and be clinically useful [27,28]. A pharmacogenomic marker of adverse events should adequately exclude from treatment those individuals likely to experience the event (i.e., avoid false negatives). Over-exclusion of patients from treatment (due to false positives) may be acceptable in situations where alternative therapies exist and the ADE to be avoided is serious. Thus, a highly prevalent marker may have utility even if the adverse event rate is very low, so long as it captures at-risk patients. However, where no alternative treatments exist, the marker should also adequately not exclude individuals who are not at risk, so that treatment is not inappropriately withheld. By virtue of these performance characteristics, investigations should prespecify clinically relevant effect sizes and performance parameters, and base the required caseload on those estimates.

Fig. 2 illustrates a potential pathway for translation of a biomarker from clinical need to clinical application. Follow-

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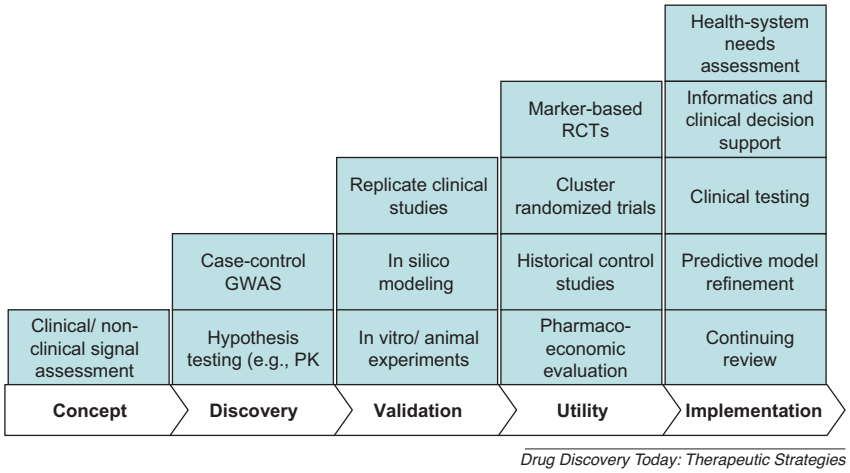

Figure 2. Translating pharmacogenomic biomarkers. Biomarker development proceeds through many phases. Upon establishing that a biomarker may have utility given a clinical need (i.e., safety signal, PK heterogeneity), exploratory analyses to discover biomarkers can be performed using existing data sources. Once a marker is identified, it can be validated in independent datasets or by way of experimental support. Where feasible, prospective trials or historical control studies can be used to evaluate whether the marker improves treatment outcomes. Upon establishing validity and/or utility, clinical testing infrastructure can be established to meet the needs of individual health-systems, with processes for improving the predictive model and continual review of its efficacy.

ing discovery, another key issue challenging translation is the ability to validate or replicate pharmacogenomic associations. If the marker is related to pharmacokinetics, to the extent that the exposure-safety relationship is well-established, confirming biomarker validity can be accomplished prospectively with small pharmacokinetic studies. For markers without a clear mechanistic link, causal inference relies on the totality of evidence from pharmacology, sound epidemiology, and other studies. For example, experimental studies supported the biological plausibility of the HLA relationship with carbamazepine-induced SJS, where in vitro studies directly implicated MHC II involvement [29]. Additionally, markers for ADEs that meet high thresholds for statistical significance are more compelling, particularly when employing GWAS or high-throughput sequencing methods. Indeed, pharmacogenomic markers derived from GWAS that had highly significant *p*-values have been often reproducible in replication populations or subsequent studies, suggesting that the common requisite of independent replication may be moot for highly significant markers with large effects [21,30,31]. In small studies, setting stringent thresholds is predicated on large effect sizes and carries a risk of Type II error, but desirable when opportunities to replicate are sparse.

Having established validity, confirming the utility of a marker in the clinical setting is a major hurdle that hinders clinical uptake of pharmacogenetic testing. Although a discovery-validation strategy has been traditionally required to establish 'believability' of pharmacogenomic associations, the evidentiary requirements for utility may need to be recalibrated based on the marker's performance and plausibility. For more common adverse outcomes, such as bleeding with warfarin or abacavir hypersensitivity, it is possible to prospectively test the effectiveness of screening strategies in making treatment decisions. A prospective randomized trial was conducted for abacavir that established the utility of the test [24], and with such strong evidence, testing was rapidly adopted in clinical practice [16]. Similar trials are ongoing for warfarin and clopidogrel with their respective biomarkers [14,32]. However, in most situations, prospective trials may be technically, economically, and/or ethically infeasible. Non-traditional study designs to demonstrate clinical utility of a pharmacogenomic intervention could involve cluster randomization, where clinical practices are randomized to whether or not to implement a testing strategy, and historical control studies, where system-wide implantation of pharmacogenetic testing can be clearly demarcated. In both scenarios, decreases in the incidence of the adverse event relative to non-tested controls, whether derived from independent centers or historical data, can be examined along with the economic impact.

With validity and utility established, implementing clinical genotyping programs to predict adverse events has numerous practical barriers from a public health perspective. Inappropriately excluding a patient from treatment due to a predicted ADE risk presents a clinical dilemma, requiring the availability of alternative treatments and knowledge that the biomarker relationship does not exist for those alternatives. That is not to say that all biomarkers must be highly predictive of an adverse event and used to make treatment decisions, because some may be more appropriately used to support the diagnosis of an adverse event (as part of the

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differential), or identify patients in whom more intensive safety monitoring is necessary.

The current paradigm relies on a drug-test pair model with clear expectations for a specific action and utility. However, use of genetic information in the clinical setting, as with any other patient-specific factor, is far more complex than this paradigm would presume. Given the rarity of many severe adverse events, broad-based screening should be economically feasible. Much of the debate concerning implementation of FVL screening, for example, focused on issues of cost-effectiveness given the marker's low prevalence and small absolute risk difference [17]. Free clinical access to individual genetic data, so that it may be considered along with other clinical factors and the treatment context, would probably circumvent many of the economic and decision-making requisites, elevating the perception of utility. This approach reframes the question – rather than asking, 'Is it worth it to *order* a pharmacogenetic test for this patient?', the question becomes 'Is it worth *using* this readily available information in my treatment of this patient?' The value of this model is currently being tested in the Coriell Personalized Medicine Collaborative [33].

Perspectives on pre- and post-approval biomarker discovery and validation

Based on the preceding examples, it is apparent that discovery of safety pharmacogenomic biomarkers is a feasible and worthwhile pursuit, notwithstanding logistical and methodological challenges. Central to all research in this area is the availability of biospecimens and careful definition of ADE phenotypes. DNA sampling from patients in clinical trials has led to the identification of safety biomarkers for simvastatin [19], abacavir [26], lumiracoxib [20], and anti-EGFR therapies (cetuximab and panitumumab) [16], among others. For some of these examples, drug developers have been able to promote enhanced use of their products through recalibrating risk/benefit (e.g., abacavir, anti-EGFR monoclonal antibodies) and engage with regulatory agencies to identify patient subsets for which their non-approved drug could potentially be approved (e.g., lumiracoxib). Throughout a drug's lifecycle, we highly recommend DNA be collected from all trial participants, or at least from targeted populations (e.g., cases of interest and controls), and stored indefinitely to permit retrospective pharmacogenomic studies. However, many barriers remain including regional heterogeneity in ethics committees and competing resources. Were the fate of a drug's marketing authorization to hinge on safety issues, genotyping strategies to mitigate risk could theoretically provide regulatory agencies with sufficient assurance to allow for drug approval or continued marketing.

ADEs related to drug concentrations can be managed by way of controlling dosing or exposure. Given a strong expectation that excessive exposure will translate to adverse events, and that metabolism via polymorphic pathway is extensive, early phase pharmacokinetic studies can be conducted to define a dose that curtails the excessive exposures in poor metabolizers of the relevant enzyme, for example. Additionally, for drugs with expected narrow margins between safety and activity/effectiveness, poor metabolizers can be excluded from first-in-human and dose-finding trials so as not to skew the maximum tolerated doses. Tailored doses may then be carried forward into Phase 2 or 3 trials, or a population-based dose can ultimately be derived after estimating the effect of genotype on final dose requirements. Often, the metabolic pathway is not well characterized, and the exposure-safety relationships are typically established over the full course of a clinical development program using population pharmacokinetic methods, modeling, and simulation [34]. In this scenario, broader DNA collection from trial participants across the development phases would be required to perform broad-based metabolism/transport genotyping. As information accumulates, prospectively designed pharmacokinetic/pharmacogenetic studies or modeling and simulation can be used to validate the pharmacogenetic relationship and define appropriate dosage for the genetic subpopulation, much in the same way that renal impairment and hepatic impairment dosing recommendations are handled. Although some drug developers feel these strategies may encumber development and the clinical use of the drug to some extent, the potential to significantly improve the risk/benefit profile may outweigh the added burden. This is especially true given that late phase attrition rates in drug development are partly related to either safety or dosing issues. Furthermore, this theoretical concern has not borne out for the majority of drug development programs that have included an exploratory pharmacogenomics component.

Pharmacogenomic studies of severe, idiosyncratic reactions in pre-approval phases are constrained simply by the incidence of the adverse event, which is often very rare or undetectable. Also, adverse events are not likely to accumulate in substantial numbers even in the course of formal post-approval trials. Although the power of DNA collection in post-approval trials has been illustrated for simvastatin-induced myopathy [19], planning for creative strategies to accrue cases and supportive data (e.g., biomarkers) should be considered in the post-approval space. Where certain safety issues are anticipated, capturing intermediate phenotype data (e.g., LFTs) and deep phenotyping (e.g., biopsy specimens) is valuable not only to support plausibility and validity of pharmacogenetic relationships, but also to increase both sample sizes (in terms of absolute patient numbers) and power to detect effects by capturing phenotype data that are mechanistically proximal to the ADE. For nonfatal events, it may be feasible to develop infrastructure that allows prospective banking of incident adverse events. To be successful in these efforts, drug developers may need to develop novel,

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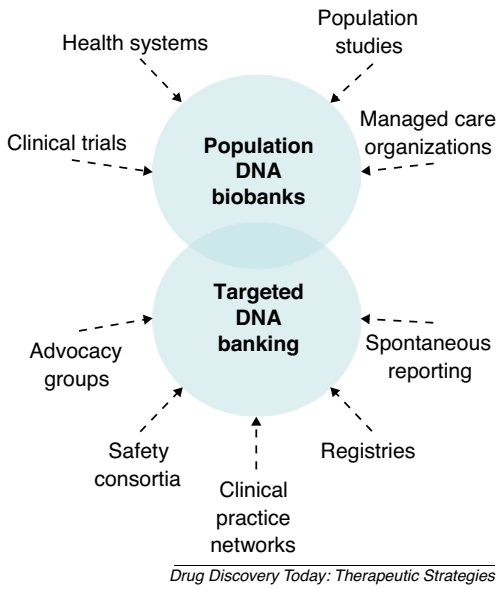

Fig. 3. Biospecimen sources. DNA samples for adverse event cases may be drawn from a variety of sources. To date, DNA specimens from cases have been collected primarily through safety consortia and clinical practice networks. Other viable strategies may include identification of cases captured through ongoing efforts such as clinical trials, population research studies, and large-scale biobanking projects within health-systems or managed care organizations. It may also be possible to proactively collect samples through post-marketing registries, and possibly even disease specific foundations or patient advocacy groups.

innovative mechanisms to facilitate and consolidate the flow of safety data.

In the post-approval space, where drug exposure and adverse event reporting are beyond the control of the drug developer, other stakeholders may need to share the responsibility of contributing to the science of drug safety (Fig. 3). The ideal pharmacovigilance model should entail broad-based, unbiased biospecimen collection from the broader population, which is necessary to capture fatal events and chronic toxicities. For example, Vanderbilt's opt out model of DNA banking coupled with an electronic medical record is a powerful prototype [35]. Others include the large-scale studies being initiated by Kaiser Permanente, Medco [36], and other health systems [37]. Large consortia such as the Serious Adverse Events Consortium, the Drug-Induced Liver Injury Network, and the Electronic Medical Records and Genomics (EMERGE) network, among others, may be necessary. These networks have had many successful outputs that have been recently published. Partnerships between payers, healthcare systems, pharmaceutical companies, and the government will be crucial to post-approval surveillance and sample collection.

Conclusions

Numerous genetic risk factors for ADEs have been successfully identified in recent years. Genotyping in early phase studies – using broad-based arrays where the metabolic pathway is not certain – may be important for prodrugs and drugs with variable PK/PD to the extent that exposure could be related to efficacy or safety. Genotype information (e.g., for ADME genes) can be prospectively applied in early phase studies so as to minimize the risk for exposure-related safety issues. However, since safety issues often do not surface until the completion of late phase clinical trials, DNA samples should be collected in all pivotal trials. An alternative may be to target sampling from clinical events of interest, such as primary efficacy endpoints or treatment-emergent adverse events. The utility of this approach, however, may be limited if the phenotypes of interest are fatal events. Candidate markers should be prespecified, where possible, and supported by biological evidence. However, the mechanistic basis of many severe adverse events is often not readily apparent. In this regard, genome-wide strategies have been productive. The totality of evidence should be considered in making decisions regarding validity and utility. In the post-approval setting, expanding the capabilities of electronic medical record-linked biobanks will be instrumental to enabling pharmacogenomics research in the safety realm. Many hurdles remain in translating safety biomarker testing to the clinic, as efficiency and economic issues should also be acknowledged. However, the ready availability of genomic information will minimize the barriers to translation as the quandary of whether or not to test a patient for a given gene–drug pair will no longer be at the heart of the issue.

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