



Equitable Discovery and Implementation of Pharmacogenomic (PGx) Testing in Cancer Care: Recommendations

Introduction

Pharmacogenomics (PGx) is the study of how inherited genomic variation is associated with the clinical effectiveness or toxicity of drugs. For example, some variants can lead to rapid metabolism of certain drugs, leading to lower systemic exposure, and potentially less effectiveness. In contrast, other variants can cause slower drug metabolism, potentially leading to toxicity, including death. This area of personalized medicine is rapidly advancing. Oncology applications of PGx testing offer patients the opportunity for customized treatments that can minimize adverse effects and maximize the therapeutic benefits of drugs used for cancer treatment and supportive care. In 2021, the Pharmacogenomics Knowledgebase (PharmGKB) database annotated 154 gene-drug pairs with actionable gene/drug interactions, of which 92 represented oncology drugs (1).

Several well-characterized examples show how PGx influences the effectiveness and safety of drugs used to treat patients with cancer. One example is the treatment of solid tumors with 5-fluorouracil (5FU), which is broken down in the liver by the enzyme dihydropyrimidine dehydrogenase (DPD) before excretion. Some patients have variants in the DPYD gene that lead to partial or full DPD deficiency, which results in a toxic buildup of 5FU after administration at standard doses. Estimates indicate that 1300 Americans die annually from toxicity after administration of 5FU (2).

Hundreds of variants have been identified in the DPYD gene, and prevalence estimates of DPYD variants leading to DPD deficiency range from 0.02–8%, with up to tenfold differences in individual variant frequency observed between populations (3-6). However, as with most human genetic studies, most data on DPYD alleles comes from studies of relatively homogenous populations of Western European ancestry (7). In addition, recent work has identified new DPYD variants prevalent in people with African genetic ancestry, highlighting that variant discovery and characterization based on limited and homogenous study populations have been inequitable. These findings illustrate the importance of studying PGx in a large and diverse population, accurately

characterizing participants' genetic ancestry to detect low-frequency genetic variants, and describing how these variants impact the safety, effectiveness, and/or pharmacokinetics of drugs.

Health disparities also exist in implementation of PGx testing and PGx-guided dose personalization, due to multiple factors including inconsistencies in drug labeling and payor coverage, inadequate evidence synthesis and available guidelines, and insufficient provider and patient awareness and education (3). Several studies have shown that PGx-guided dosing of clinically actionable variants can decrease toxicity and offer cost savings (8, 9). Ongoing PGx implementation projects are mainly limited to academic medical centers in urban areas; focused efforts are needed in rural and underserved areas. As the PGx field continues to expand, it is crucial at this juncture to identify and address the sources of disparities and inequity in PGx discovery and application.



Testing for somatic genetic variants is now the standard of care in treatment of many solid tumors, so the field of oncology is poised to expand and integrate germline genetic variant testing. Oncologists can be leaders in incorporating equitable PGx testing for cancer care, paving the way for expansion to other disciplines. The following consensus recommendations were developed by a working group convened by ACS CAN and are endorsed by the stakeholders listed at the end of this document. These recommendations address various challenges and encourage both programmatic activities and policy changes to ensure that all cancer patients can benefit from PGx advances.

Recommendations



1. Diversify Oncology Research Participation

To reduce bias and accurately evaluate the efficacy and safety of medical treatments in the intended population, clinical trials should include the participation of patients representative of different racial, ethnic, and other underrepresented populations to accurately account for the diverse characteristics and experiences of individual patients. Factors influencing disease risk and treatment response include demographics, lifestyle, environment, underlying medical conditions, and genetic variation. Particularly important for understanding PGx-driven differences is genetic ancestry. While many oncology clinical trials are underpowered to discover subgroup differences that may be driven by PGx drug-gene associations, diverse participation can generate data that can help identify unusual subpopulation-specific signals, which can be further explored using a variety of tools.

Recommendation: Sponsors should ensure diverse ancestral group participation in clinical trials per the epidemiology of the disease in alignment with existing FDA guidance on inclusion of racial and ethnic groups. Data or samples that can be used to evaluate interactions with potential pharmacogenes should be collected. In cases where prior evidence has suggested potential PGx impacts, especially differential impacts between subgroups, research plans should be formulated to clearly define such differences. FDA should provide additional guidance for methods outside of registrational trials for exploring PGx differences, such as using in-vitro assays, mining genetic databases, collecting real-world data (RWD), or other methods.

2. Improve Databases to Foster Discovery

2a. Improve Diversity in Databases

The databases used for many genomic studies are largely biased toward data from individuals of Western European descent. Identifying alleles with altered function often requires thousands of representative individuals, and sometimes even more for rare variants. Without substantial inclusion of data from patients with diverse genetic ancestries, it may be difficult or impossible to identify variants unique to specific ancestral groups, creating an identification bias of variants found only in individuals of Western European descent. Over the last 10-15 years, databases have shifted to include more populations with Asian ancestry (a designation that itself represents a very heterogeneous group). However, there is still a need to increase genomic database diversity by expanding representation from diverse and understudied populations of shared genetic ancestry.

Recommendation: Databases used for PGx discovery and data collection should include sufficiently large numbers of individuals from non-European ancestries to power inclusive and appropriately diverse PGx discovery in all ancestries. Therefore, it is critical to examine, highlight, and account for disparities in existing RWD sources when used in identifying PGx variants, and purposefully and prospectively collect data from communities traditionally underrepresented in such data sources to fill gaps in existing databases and to develop new data sources. Obtaining a sufficient quantity of patients with diverse genetic ancestry will be aided by global database sharing, especially in non-European settings. Clarity and consistency in population and ancestry descriptions are also needed.

Recommendations

2b. Combine Pharmacogenomic, Treatment, and Outcomes Data in Databases

Given limitations in the ability to discover new PGx effects in prospective clinical trials that are primarily focused on proof of efficacy, it will be critical to leverage large datasets of existing data collected as part of prospective registries and/or compiled from RWD such as electronic health records (EHRs) or insurance claims data. To be most effective, the data must include information related to genetics, oncology treatments, and outcomes, and must be robust enough to draw conclusions about how these factors are connected. Unfortunately, while large volumes of data exist in various databases, few databases combine all three data elements in sufficient volume to facilitate discovery.

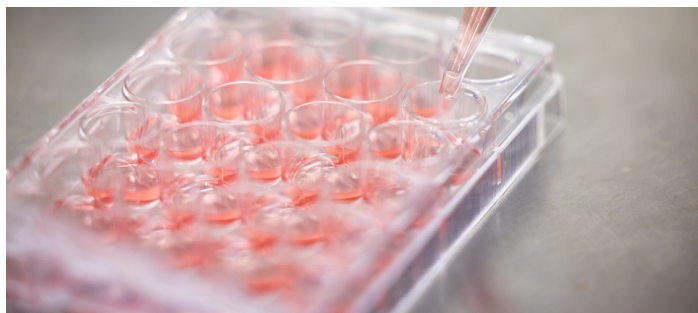
Recommendation: Existing databases should be augmented via purposeful and prospective collection of PGx data and/or linked with each other to provide PGx germline genetic data, drug administration, and outcomes data on individuals with cancer. Databases may include prospective registries, archived clinical trial data, claims data, patient-submitted data, or RWD from practice EHRs. Data needs to be deidentified to respect privacy and structured in a way that aligns across sources and allows for aggregation, which will require active efforts towards harmonizing data standards.

2c. Leverage Adverse Event Reporting Infrastructure

Although adverse drug events (ADEs) are one of the leading causes of death, the adverse event reporting system has not been modernized since the late 1990s. As a result, recent studies suggest that clinically relevant adverse drug reactions are currently dramatically underreported (10). Moreover, ADE data, in combination with genetic variant and treatment data, can be used to build and strengthen the evidence of clinical validity and utility of PGx drug-gene association information for guiding appropriate treatment decisions. For already validated PGx associations, ADE data can be used to inform (or reconsider) treatment decisions if PGx info still needs to be considered. ADE data can also be used in

combination with demographic data to help identify existing sub-population disparities in drug-gene associations and help inform appropriate testing policies.

Recommendation: Remove barriers to ADE reporting, including creating accessible reporting systems integrated with the EHR and compatible with provider workflow. Data indicating and describing ADEs should be thoroughly and systematically collected in reporting databases such as FDA's Adverse Event Reporting System.



3. Leverage Drug Labels to Communicate Known PGx Impacts

3a. Improve Consistency, Completeness, and Location of PGx Information in Drug Labels

Every FDA-approved drug is accompanied by a label that synthesizes information to be used by healthcare providers, patients and caregivers when using the drug. PGx data can often be found in several of the 17 sections typically found in a label and provide an important resource for communicating PGx concerns related to a specific drug. However, despite guidance recommending placement of PGx information, the label locations can be inconsistent across drugs. In an example of two different drugs with the same active ingredient (Carac and fluorouracil), one label includes a PGx-related contraindication while the other does not (11, 12). Similarly, some drugs include information about population-specific PGx variant frequencies, while others do not.

Patients would not typically be aware of potential drug-gene interactions absent guidance from their healthcare provider. Therefore, providers are an important source of information that can empower patients in their decision-making. FDA labels include a specific "Patient Counseling

Recommendations

Information” section, which according to FDA “...typically focuses on major risks of the drug and, when appropriate, how the patient may mitigate or manage these risks” (13). However, patient counseling information related to PGx in oncology drugs appears inconsistently.

Recommendation: FDA should update guidance for the consistent location of PGx information on drug labeling, making a stronger recommendation for inclusion of safety-related information in the Warnings and Precautions, Contraindications, and Patient Counseling Information sections when PGx interactions could lead to serious and adverse events. Inclusion of information in the patient counseling information section is especially critical when a drug has PGx-related risks that could be avoided or mitigated via testing or enhanced vigilance. FDA should also encourage the inclusion of information on the prevalence of variants by subpopulation when known.

3b. Keep Labels Current with PGx-Related Safety Information

Labels for new drugs are proposed by drug sponsors and reviewed and approved by FDA based on guidance around standard formatting and content. Sponsors can update labels later as new information about a drug evolves. When drugs are off-patent with generic equivalents, the drug labels of the generic versions must match the original reference drug. The original sponsor still controls the label but typically has reduced incentive to keep the label up to date. While proposed label changes must typically come from sponsors, one exception concerns safety-related changes, in which FDA can initiate the process and require sponsors to adopt label changes (14). Since many drug-gene interactions carry safety considerations, FDA’s ability to require label updates is one method for ensuring PGx-related information continues to be updated on labels even for older drugs.

Recommendation: In situations where established PGx-related safety issues have not been otherwise incorporated into a drug’s label, FDA should take steps to update labels through voluntary processes like Project Renewal (15) or by exercising its authority to compel relevant safety updates.

4. Incorporate PGx Testing Recommendations into Treatment Guidelines

Treatment guidelines, like those generated by the National Comprehensive Cancer Network (NCCN) or ASCO, are important drivers of clinical practice. However, while such guidelines have generally incorporated recommendations for somatic tumor testing as the scientific evidence advances, they make less mention of proactive PGx testing and potential treatment modifications, despite drug-gene interactions playing a role in modulating the safety and efficacy of oncology and supportive care drugs.

Recommendation: Treatment guideline authors are encouraged to incorporate PGx testing recommendations into their guidelines in accordance with current evidence.

5. Improve Coverage of PGx Testing

Payor coverage plays a large role in provider uptake and patient access to PGx testing. However, current coverage of PGx tests relevant to oncology patients is low, even in cases where clinical validity is well established and drug-gene associations are included in FDA labels or are assigned CPIC guideline level A or B. In addition, coverage is inconsistent among the multiple public and private payors in the U.S. healthcare system, with more favorable coverage for those covered under Medicare as compared to Medicaid and non-Medicare commercial payors.

Recommendation: Enact policies to ensure coverage for PGx testing when it is supported by medical and scientific evidence, including, but not limited to, labeled indications for an FDA-approved or -cleared test; indicated tests for an FDA-approved drug; warnings and precautions on FDA-approved drug labels; Centers for Medicare and Medicaid Services (CMS) National Coverage Determinations or Medicare Administrative Contractor (MAC) Local Coverage Determinations; or nationally recognized clinical practice guidelines and consensus statements.

Recommendations

6. Improve Infrastructure Resources for Incorporation of Oncology PGx Programs

PGx test results impact medication decisions for the rest of a patient's life, making discrete storage of results with interoperable sharing across systems vital. A few academic medical centers have invested in clinical decision support tools (CDST) that alert prescribers when PGx results have evidence-based drug or dose change guidance for pending prescriptions. Unfortunately, CDST technology adoption has not extended to many health systems where most patients receive care. Integrating drug-gene association data in EHR, CDST, and research databases will also allow capturing of real-world evidence that can reveal correlations with drug and dose optimization, including within populations of genetic ancestries that have historically not been well represented in clinical trials.

Recommendation: Drive EHRs toward the increased ability to support PGx decisions for a patient across healthcare providers, pharmacies, and laboratories when making prescribing decisions. This will require interoperable EHRs, leveraging data standards, and the use of CDSTs linking PGx tests with medication use and prescribing. Additionally, sufficient guidance should be made available for implementing and effectively utilizing these systems, and ensuring that they are scalable in various environments.

7. Ensure PGx Tests Include Relevant Variants

PGx tests range from single gene, single variant assays to next-generation sequencing panels of multiple genes. In most cases, multiple variants exist that can indicate altered drug safety or efficacy, and certain variants are more common in individuals with specific ancestries than others. Therefore, tests that omit variants known to alter drug metabolism may fail to identify potential issues with a drug. If omitted variants are enriched in certain populations, those populations may experience disparate outcomes relative to others.

Recommendation: PGx testing should cover all clinically validated variants supported by high-quality evidence

relevant to the prescribing situation for which the testing is being ordered. Special care should be taken to include variants relevant to non-European ancestral groups. Tests should be updated to include additional variants if new PGx associations are discovered, and any variants included in a test that lack clear evidence of clinical relevance should be clearly noted in the test report.

8. Create Incentives for Appropriate PGx Testing

While PGx program implementation has been demonstrated to reduce system costs and improve outcomes (16, 17), the benefits of those savings are not always shared with providers or institutions responsible for implementing such programs. Quality metrics, provider or institutional incentives, and accreditation programs provide more direct incentives to agents within the healthcare system that influence testing decisions and have long been used as tools to drive improvements in healthcare practices.

Recommendation: Consider the development of quality measures for inclusion in CMS payment programs or Healthcare Effectiveness Data and Information Set (HEDIS) that reward guideline-concordant use of PGx testing in the cancer setting. Additionally, third-party quality assessment or accreditation programs such as ASCO's QOPI measures or the American College of Surgeons' Commission on Cancer accreditation program are encouraged to incorporate appropriate PGx testing into their evaluations.



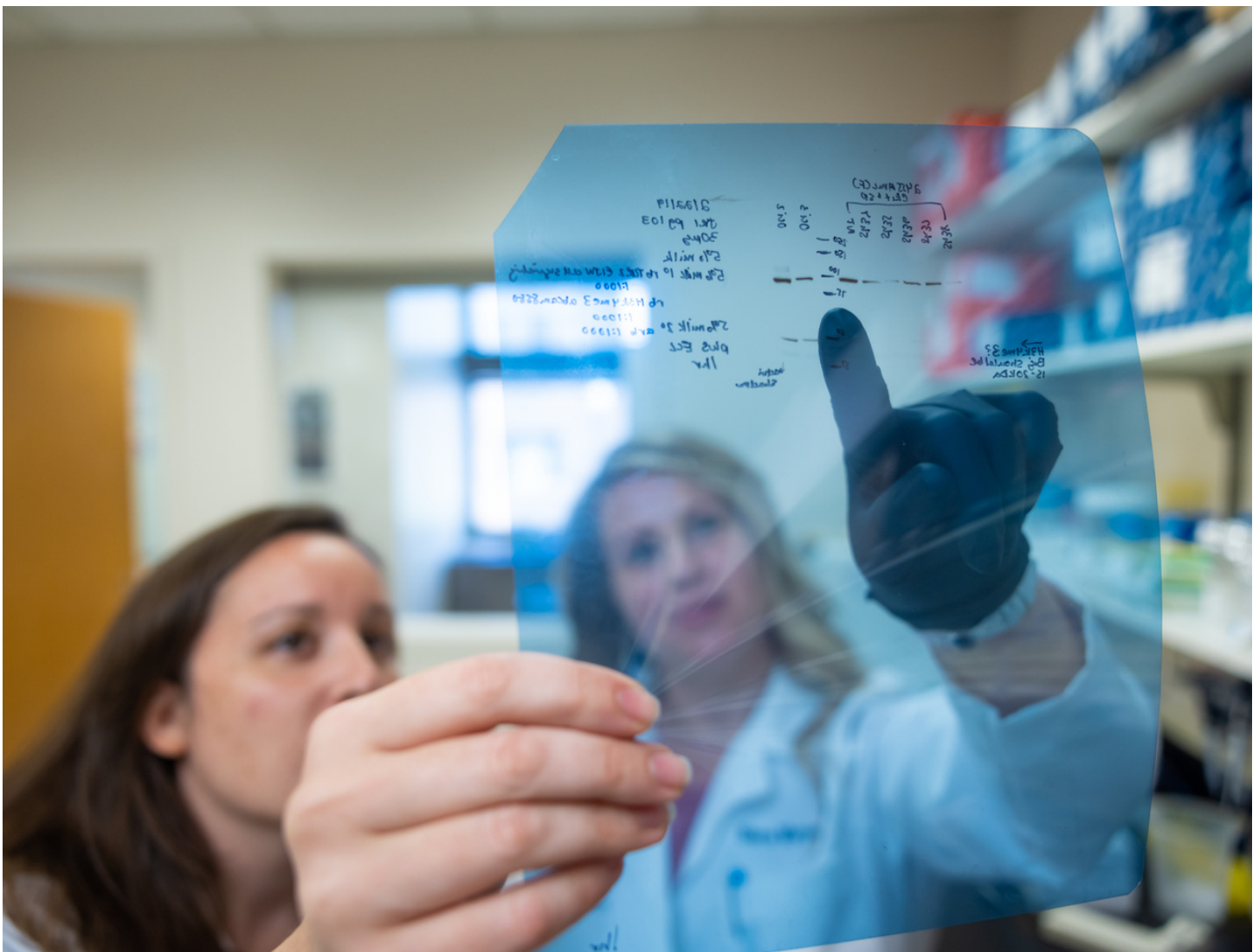
Recommendations

9. Assess and Improve Education and Awareness of PGx Testing and Implementation

Equitable clinical implementation of PGx testing and knowledge depends on clinicians having sufficient understanding of genetics and PGx to make informed decisions about PGx testing, interpretation of results, and appropriate prescribing modifications. It has been shown that while clinicians find PGx useful, they lack the knowledge to implement it effectively (18).

Recommendation: Assess and improve PGx knowledge and awareness among clinicians. This can be achieved through medical education, continuing education, and more general educational and awareness campaigns. Targeted knowledge and awareness should include context for PGx testing, ancestral differences in PGx characteristics, ability to act on PGx test results, and the detection and reporting of potential PGx-related adverse events.

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