Barriers, solutions, and effect of using pharmacogenomics data to support opioid prescribing

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SUMMARY

Opioid use and misuse are continued issues facing clinicians across all aspects of health care. As clinicians struggle to effectively manage opioid prescribing, pharmacogenomics (PGx) further offers the prescriber an improved ability to understand the potential for an individual patient's genetics to influence opioid efficacy and safety. When PGx data are available at the point of initial prescribing, clinicians can apply that data to drug therapy selection. However, barriers continue to exist relative to PGx data sharing and interpretation, which have created difficulties for widespread PGx implementation. This article briefly describes potential barriers to PGx data integration, strategies to overcome those barriers, and the potential positive effect of successful data sharing on opioid prescribing.

Prescription drug monitoring programs (PDMPs) have been successfully operationalized to share controlled substance prescribing data across health care settings. Such

data sharing enables clinicians to, among other things, better understand risks associated with misuse. Because a relatively limited volume of PGx data is currently pertinent to opioid prescribing, such PGx data could be added to PDMPs as a way to communicate genetic information within current technology platforms. Not only would this integrate into existing clinical workflow models where PDMP data are accessed at this point of prescribing and/or dispensing, but associated clinical guidance for PGx data interpretation in the context of opioids could be integrated into the workflow process. Such clinical decision support could be provided directly through the PDMP interface for uniformity or could be provided via systems that access PDMP data. Clinical, economic, and policy implications of the inclusion of PGx data within PDMPs are also discussed. Through harnessing PDMP for data sharing, multiple barriers to PGx implementation could be mitigated, and clinicians may have better access to PGx data to optimize opioid prescribing.

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The opioid epidemic in the United States has resulted in nearly 450,000 deaths from 1999 to 2018.¹ Although opioid dispensing has decreased 13.5% since 2017, more than 168 million opioid prescriptions were dispensed in the United States in 2018, signaling that the country has not yet solved the epidemic.^{1,2} As the safety of opioid use is being called into question,

the contribution of genetic factors to opioid efficacy and safety has been increasingly studied. Knowing that some patients have genetic variations that code for changes in drug metabolism, and knowing that many opioids are metabolized by the enzyme CYP2D6 into either active or inactive metabolites, the science of pharmacogenomics (PGx) can be harnessed to

better predict safety and efficacy outcomes for some opioids.

Not only have multiple studies described a link between PGx and clinical outcomes for pain management,^{3,4} but similar studies have reflected positive clinical outcomes following PGx-guided management for other conditions.^{5,6} Clinical pharmacogenomic guidelines are available

that suggest specific recommendations for codeine, tramadol, and other opioids.⁷ Similarly, the U.S. Food and Drug Administration (FDA) table of pharmacogenetic associations includes codeine and tramadol as medications with therapeutic management recommendations for PGx.⁸ When preemptive PGx data are available at the point of prescribing, clinical guidelines can be immediately applied to optimize prescribing.⁹ Therefore, PGx data sharing has strong potential for optimizing opioid management.

Prescription drug monitoring programs (PDMPs) are state-run electronic databases that compile the controlled substance prescribing and histories of patients and are used by all states except Missouri. Physicians, pharmacists, and other health care professionals are able to search the PDMP by patient to help with optimization of controlled substance prescribing. The information found on the PDMP can aid in determining if there are prescribing patterns that indicate a need for further investigation as to opioid misuse risk. For this reason, several states have enacted policies that require physicians and pharmacists to view the PDMP before prescribing and dispensing controlled medications.¹⁰

Policy and accessibility have driven strong usage of PDMPs to guide opioid prescribing. However, limited progress has been made towards widespread use of PGx data in a way that can help optimize opioid prescribing. PGx data have been stored via some electronic health records (EHR) systems, but data are not consistently shared with professionals in other health systems or community pharmacies. Work is being done to foster better data sharing, and related recommendations to standardize data sharing may help ease this process.¹¹ We contend that PDMPs have strong momentum to create a logical location for PGx data sharing and should be considered as a way to share CYP2D6 polymorphism data across practice settings for the purpose of optimizing opioid prescribing.

The purpose of this Viewpoints article is to briefly describe potential barriers to PGx data integration, strategies to overcome those barriers, and the potential positive effect of successful data sharing on opioid prescribing.

Practical Barriers to PGx Integration

No change to health care operations will be free from implementation hurdles, and as one might expect, unique barriers exist to PGx integration. While PGx general implementation barriers have been frequently cited in the literature,^{9,11,12} key barriers with potential for mitigation through PDMP/PGx integration are briefly outlined here.

EHR INTEGRATION

There are many barriers to the integration of PGx data in EHRs.¹¹ Depending on how much genetic data one would want to store in an EHR, there are storage space considerations and display considerations, among many others. Not only are there implementation costs, but maintenance of PGx-related information technology may be resource intensive. Additionally, PGx data would ideally need to be imported in a usable format.

DATA SHARING AND INTEROPERABILITY

While some reports of successful integration of PGx into practice have involved on-site PGx testing in a hospital,^{13,14} dissemination of this model has been limited as not all health systems are capable of on-site PGx testing. Additionally, testing at the point of care may become increasingly wasteful, since patients are more likely to have previously received PGx testing. Since PGx data do not change across one's lifespan, repeated testing may have limited utility. Finally, with increased laboratory-based and direct-to-consumer PGx testing,¹⁵ patients may bring in their own PGx results to any number of clinicians that may need the ability to input that data for other health care professionals to review.

The accessibility and trust of community pharmacists,^{16,17} coupled with the direct-to-consumer sales of PGx products in many community pharmacies, creates an interesting intersection for PGx-related clinical work. Implementation of PGx has not been widely explored in the community pharmacy setting despite the broad availability of PGx test kits in many community pharmacies.¹⁵ Unfortunately, the lack of data sharing between community pharmacists and other clinicians risks clinical recommendations that are contrary to PGx guidance, and the number of EHRs and pharmacy-dispensing systems makes interoperability quite challenging. Data-sharing strategies must not only work between health systems' EHRs, but they must also work between EHRs and community pharmacy-dispensing software systems.

PDMPs are one of the few platforms that offer existing interoperability in this way. It is worth noting that state law and administrative rules are typically and necessarily prescriptive as to the nature of the information that may be stored in a PDMP as is necessitated by the sensitive nature of the data stored in these systems, so related health policy issues would need to be carefully considered before implementation of additional data storage and sharing.

CLINICAL DECISION SUPPORT

Despite the previously mentioned guidelines that can assist with PGx-guided opioid optimization,⁷ many health care disciplines, including nurses and providers, feel PGx results

would be helpful, but they do not always feel they have adequate knowledge to use PGx results for clinical care, perhaps due in part to the rapid pace of evidence generation.¹⁸⁻²¹ Given how new the science of PGx is related to clinical practice, many pharmacists lack confidence and do not feel properly educated to interpret PGx results and may not be aware that Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines exist.^{22,23} Similar issues may exist for other clinicians. Clinical decision support (CDS) resources may help clinicians more effectively use PGx in clinical practice.²⁴

Proposed Solution: PDMPs

There is obvious potential utility to having large genetic datasets available to clinicians of many different specialties. However, with approximately 3 billion base pairs of genetic data that could be considered for genetic testing, datasets have the potential to become unwieldy. According to the most recent CPIC guidelines for codeine and other opioids, only CYP2D6 has current clinical relevance to guide prescribing at this time.⁷ Furthermore, CPIC has delineated standardized nomenclature for PGx across health care settings, meaning that there are now consistent phenotypes for CYP2D6 genetic data.²⁵ With limited reporting options with standard terminology and abbreviations, specific CYP2D6 data sharing may be much simpler than the work involved with sharing 3 billion base pairs worth of information.

Regarding EHR integration, certain challenges arise in the integration and interpretation of PGx data. Whereas current challenges exist in the flow of information between pharmacy-dispensing systems and EHRs, these same challenges would apply to the handling of PGx datasets. Indirect integration through an intermediary system, such as PDMPs, may provide a short-term solution via nonspecific alerts prompting clinicians to review PGx data profiles in more detail.

Regarding data sharing and interoperability, a drop-down menu could be added to state PDMPs that could allow data input by any clinician with PDMP access. Because CPIC guidance exists for each phenotype, a clinical significance statement could be formulated within the PDMP. Other tools to alert clinicians to this information, such as color coding, could additionally be used to highlight more actionable needs and FDA boxed warning information. As additional PGx data become clinically relevant in the future,²⁶ this model would allow for additional drop-down menus to be added in a consistent fashion. Because many EHRs and community pharmacy-dispensing systems already share data (pull and push) with PDMPs, connecting one more field

TABLE 1 Phenotype Reporting Example^{7,25}

Phenotype	Abbreviation	Clinical Significance
Poor metabolizer	PM	Avoid codeine. Tramadol, hydrocodone, and oxycodone may not be good alternatives.
Intermediate metabolizer	IM	Use label-recommended age/weight-based dosing.
Normal metabolizer	NM	Use label-recommended age/weight-based dosing.
Ultrarapid metabolizer	UM	Avoid codeine. Tramadol, hydrocodone, and oxycodone may not be good alternatives.
Indeterminate ^a	IND	Pharmacogenetic testing has not clearly indicated a phenotype.
Not available	N/A	No pharmacogenetic data are available.

^aAdditional brief explanations and/or links may be provided to assist with interpretation of these results.

of PGx information may not be an insurmountable barrier for PGx data sharing.

Regarding clinical decision support and health care professional knowledge of PGx, the EHR and pharmacy-dispensing systems may be able to assist with some level of clinical decision support, such as pop-up notifications, drug utilization review messages, and/or hard stops for prescribing or dispensing once PGx data are consistently coded and available. Table 1 offers a visual example of brief notes that could trigger a clinician toward more substantive review of the PGx information if relevant for a specific patient.²⁷

Potential Effect of PDMP-Based Data Sharing: Clinical, Economic, Policy, and Patients

CLINICAL

Treatment of pain can be one of the greatest challenges of a clinician with no clear solution. Personalization of care is paramount, as there can be physical, psychological, and emotional aspects to the pain, and there are often both drug and nondrug treatments that can help. Side effects, drug interactions, and cost considerations further complicate the issue. PGx data clearly does not replace good clinical decision making, but the ability to guide pain management with PGx is promising. Clinical decision support tools could help to translate PGx data for clinicians otherwise uncomfortable with providing PGx-guided care.

Given that one of the stated purposes of the PDMP is to assist in clinical decision making regarding the appropriateness of controlled substance use, integration of PGx data that may help to optimize opioid selection is highly appropriate from a clinical standpoint. This rationale can be seen in the rollout of supplemental features in existing PDMPs, such as the NARxCHECK feature in the Appriss platform (PMP AWARe), an algorithm which calculates probability for unsafe use.

ECONOMIC

Although PGx testing costs have decreased dramatically in recent years,^{9,28} the question of who would most benefit from PGx has not been fully answered, but test volume and related PGx data available have increased substantially. This proposed solution would not require that additional PGx testing be completed; instead, it would seek to capture already generated PGx data and share that with other health care professionals who could possibly benefit from the use of that data so that the value of the data could be maximized. Because genetic testing results are unchanged throughout a person's lifetime and different results would not be expected with repeat testing, strategic data sharing may reduce the risk that another health care professional may unnecessarily repeat a PGx test and increase the total cost of care. Therefore, capturing preexisting PGx data in a way that is easily accessible by all health care professionals has the potential to not only reduce the cost of repeat testing, but also to make sure that all data are able to be used when needed.

POLICY

Analysis of state-specific, existing regulation regarding PDMP access, type and scope of data storage, and data security would be warranted before widespread implementation of any policy that would allow the sharing of PGx information. Such work may help to identify viability within a specific state's framework and may help to inform decisions that would need to be made regarding the handling of PGx data. While PGx phenotype could functionally be incorporated into demographic tables of a database, this approach would limit the ability of systems to exchange information via common data-sharing standards (e.g., Health Level Seven International standards and National Council for Prescription Drug Programs), since PGx phenotypes are not commonly recognized demographic fields. Classifying and storing the data using pharmacogenomic data structures are also feasible, but this approach would likely necessitate a more extensive build-out on existing PDMP systems. Coordination with groups that are working on coding approaches would be prudent to ensure

consistency of approach and best chances of data sharing between PDMPs and other software systems.

In order to minimize fragmentation in the way PGx data are stored within pharmacy and medical systems, it is imperative that a robust system for the storage and transfer of this data between systems be developed. Also, it should be recognized that, should the incorporation of PGx phenotypes be introduced into demographic datasets, this would merely serve as a stopgap measure until a more comprehensive solution becomes tenable.

PATIENTS

Incorporating genetic data into the PDMP may not seem to be substantially effective for a majority of patients, given that approximately 10% of patients would be expected to exhibit a CYP2D6 ultra-rapid metabolizer or poor metabolizer phenotype. However, for poor and ultra-rapid metabolizers, it may be useful in determining predicted efficacy, as well as potential for life-threatening events such as respiratory depression for certain opioids.

Conversely, for the other 90% of patients, there may be some reassurance that the patient is to expect a typical response from a typical dose, and no issues would be expected specifically due to PGx. Knowing that a patient is a normal metabolizer has allowed for additional options to be made available for opioid use in some patients.²⁹

Knowing that privacy is a common concern related to PGx, it is helpful to understand that access to PDMPs is generally restricted to registered health professionals, and we suggest including the minimally necessary information for guiding clinical decisions (i.e., CYP2D6 phenotype). In this way, the potential for misuse of the data is minimal. Additionally, other protections exist, such as the Genetic Information Nondiscrimination Act.³⁰ Communicating these protections may help clinicians and patients be more willing to embrace the sharing of PGx data.

CONSIDERATIONS FOR IMPLEMENTATION AND ASSOCIATED LIMITATIONS

Any change to pathways for data sharing requires time and cost so must be carefully considered before implementation. Not only must the change be weighed against modifications that could affect other areas of care, but it must be weighed against other potential solutions for PGx management. When comparing with other PGx strategies, there is strong logic in suggesting that more PGx data should be shared than simply CYP2D6 phenotype information and that uniform coding practices be used. Calls for such integration have been well documented.²⁴ Unfortunately, such integration is still lacking in many health care practices; therefore, limited PGx data sharing through PDMPs may serve as a

temporary stopgap to assist while waiting for full-scale PGx integration.

There is an inherent risk of a stopgap being “good enough” to limit further integration. On the other hand, there is also the potential for clinicians to begin to appreciate PGx data more once they are used in limited circumstances (e.g., pain management) and request increased PGx integration for other disease states.

Conclusions

As a stopgap in the quest for more comprehensive EHR interoperability, sharing PGx data via PDMPs provides a logical and more rapidly achievable solution for PGx data sharing so that opioid prescribing can be further optimized. Specific incorporation of CYP2D6 PGx data into PDMPs has the potential to be a minimally invasive PDMP edit that may improve patient care and reduce costs through reducing the risk of unnecessary repeat testing. Further PGx data, if determined to be clinically relevant in the future, could similarly be added. States should strongly consider incorporation of CYP2D6 PGx information within their PDMPs to help improve opioid prescribing.

DISCLOSURES

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