Engaging pharmacogenomics in pain management and opioid selection

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Opioid misuse and mismanagement has been a public health crisis for several years. Pharmacogenomics (PGx) has been proposed as another tool to enhance opioid selection and optimization, with recent studies demonstrating successful implementation and outcomes. However, broad engagement with PGx for opioid management is presently limited. The purpose of this article is to highlight a series of barriers to PGx implementation within the specific context of opioid management. Areas of advancement needed for more robust pharmacogenomic engagement with opioids will be discussed, including clinical and economic research needs, education and training needs, policy and public health considerations, as well as legal and ethical issues. Continuing efforts to address these issues may help to further operationalize PGx toward improving opioid use.

In 2017, the opioid crisis officially became a public health emergency as deeply troubling statistics were observed across the country [1]. While opioid prescribing has declined from a peak around 2010–2012, morphine milligram equivalents of opioids prescribed per person are roughly triple what they were 20 years ago [2]. Further, roughly 21–29% of those prescribed opioids for chronic pain misuse them and between 8 and 12% develop opioid use disorder [3].

One of the five points in the US Department of Health & Human Services Response to the Opioid Crisis is to advance the practice of pain management enabling access to high-quality, evidence-based pain care [4]. Resources have recently been developed, such as the CDC Guideline for Prescribing Opioids with Chronic Pain, to assist with improving prescribing practices [5]. In addition, an increased use of state-level prescription drug monitoring programs has been associated with opioid prescribing reductions [6], and an increase in the use of naloxone prescriptions has been recently observed [7]. Despite these positive advances in opioid management, 2017 data suggests there were 58 opioid prescriptions per every 100 Americans [8], and overdose deaths have accelerated during the COVID-19 pandemic [9].

The field of pharmacogenomics (PGx), or the science of the relationship between a person's genetic attributes and drug response, has seen tremendous growth in the past few years. The first guidelines relating to opioid prescribing from the Clinical Pharmacogenetics Implementation Consortium (CPIC) were released nearly 10 years ago. Updated in late 2020 with more recent literature, these clinical guidelines now provide more precise recommendations for codeine, tramadol and hydrocodone prescribing as it pertains to different CYP2D6 phenotypes [10]. While there is potential for improved opioid management through PGx, as well as several practice-based examples of PGx-guided opioid optimization, these practices have yet to become mainstream [11,12]. Despite considerable progress, barriers remain to the widespread implementation of PGx within the context of opioid management [13,14].

Future Medicine

The purpose of this article is to highlight example practices to illustrate the vision of opioid optimization through PGx while discussing barriers to PGx implementation in this context. Areas of advancement needed for more robust pharmacogenomic engagement with opioids will be discussed, including clinical and economic research needs, education and training needs, policy and public health considerations and legal and ethical issues. Each area of discussion will conclude with a specific belief or actionable step pertaining to how PGx can be advanced to further assist with opioid optimization.

Emerging practice models

While PGx is not widely observed as a key part of the clinical care process across the USA, several examples of practice models have been described in the literature where PGx information is routinely applied to patient care across inpatient and outpatient practice settings. The University of Florida began offering *CYP2C19* testing in 2012 for percutaneous coronary intervention patients to assist with antiplatelet selection and optimization [15]. Further expansion to other drug-gene pairs, such as *CYP2D6*-opioids and *CYP2D6*/*CYP2C19*-antidepressants, followed over the next few years. Best Practice Advisories, a form of clinical decision support (CDS), were built into the electronic health record (EHR) for selected drug-gene pairs. A PGx outpatient consult service has also been implemented [16]. More specifically related to opioid optimization, recent literature more thoroughly describes implementation efforts specific to optimizing postsurgical pain management through PGx [11].

Similar to the University of Florida, Sanford Health's precision medicine program, Imagenetics, also utilizes CDS tools. Clinical PGx pharmacists at Sanford provide a retrospective review once PGx test results are signed out into the EHR. Pharmacists review for drug–gene interactions and evaluate for any medications that are relevant enzyme inhibitors or inducers. A chart note is written with any recommendations. Depending on patient-specific variables, recommendations may be limited to monitoring suggestions, or no interventions may be recommended at all. After initial review, because PGx results are incorporated as a discrete value, CDS is the main approach to alert prescribers to any drug–gene interactions. CDS alerts include a description of the interaction, a link to associated CPIC guidelines, and relevant recommendations. PGx CDS is branded with 'Sanford Imagenetics' to inform providers about the nature of the alert [12]. Specific to opioid optimization, language includes considering nonopioid medications if appropriate, including opioid alternatives not dependent on CYP2D6, and lists opioid alternatives with uncertain toxicity (i.e., hydrocodone and oxycodone) [10]. Additionally, the alert has the option to keep or remove the order for the opioid prescribed. Figure 1 provides examples of CDS tools.

Community pharmacy-focused examples exist as well [17–19], with multiple publications suggesting community pharmacy as a good fit for clinical PGx management [20,21]. However, in a similar fashion to other clinical settings, implementation is not widespread. Increasing reliance on community pharmacy models may help in areas where hospitals do not have the infrastructure to support in-house PGx testing. In this approach, smaller community hospitals could collect PGx samples, send off to an off-site PGx laboratory, with results communicated back to the community pharmacist to manage follow-up with any/all involved providers. In this way, expansion to different health systems in a variety of geographies could be more easily accomplished. One additional potential positive influencer for increased uptake of PGx in community pharmacy settings may be the widespread availability of direct-to-consumer PGx testing that is available for sale in many community pharmacies. Such availability may create a need for community pharmacists to counsel patients on direct-to-consumer PGx testing [22].

These emerging practice models have shown promise for leveraging PGx in a variety of clinical settings to optimize medication use in general, with more specific and positive demonstration that pertains to opioid management. Evidence is not isolated to a single study or case report. Instead, replication in different healthcare environments implies that there is potential for PGx guidance to positively impact opioid selection in many settings. We believe that replicating these emerging models of successful PGx implementation should be strongly considered to serve more patients.

Research driving clinical practice

CYP2D6 plays a role in the metabolism of many opioids; *CYP2D6* polymorphisms can affect clinical efficacy and safety with opioid use. Additionally, CYP2B6 and CYP3A are other CYP pathways involved in opioid metabolism but lack evidence-provoking associated clinical recommendations, providing an opportunity for more research. CPIC guidelines provide therapeutic recommendations for *CYP2D6* with codeine and tramadol. The data for *CYP2D6* is not as strong for hydrocodone, oxycodone and methadone [10]. Therefore, some of the most commonly used opioids do not have PGx therapeutic recommendations at this time. Further research needs to explore the

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Best practice advisory

SANF⊇RD imagenetics

Based on this patient's genetics:

Codeine containing products and tramadol are not recommended due to lack of efficacy.

⚠ Non-opioid analgesics such as NSAID's and COX2 inhibitors should be considered based on type, severity, and chronicity of pain.

Opioid alternatives include: tapentadol, morphine, fentanyl, hydromorphone and oxymorphone. Opioid alternatives with uncertain toxicity for this patient include hydrocodone and oxycodone.

Reference: Crews et al, guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy. December 2020.

Remove the following orders?

Remove	Keep

⌂ Acetaminophen with codeine (TYLENOL WITH CODEINE) 120 mg–12 mg/5 ml oral solution
Take by mouth every 6 hours as needed for up to 3 days, Disp-180 ml, R-0, e-Prescribing, maximum MEDD: Unknown for this order

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Best practice advisory

SANF⊇RD imagenetics

Based on this patient's genetics:

Tramadol and codeine containing products are not recommended due to lack of efficacy.

⚠ Non-opioid analgesics such as NSAID's and COX2 inhibitors should be considered based on type, severity, and chronicity of pain.

Opioid alternatives include: tapentadol, morphine, fentanyl, hydromorphone and oxymorphone. Opioid alternatives with uncertain toxicity for this patient include hydrocodone and oxycodone.

Reference: Crews, et al, guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy. December 2020.

Remove the following orders?

Remove	Keep

⌂ traMADol (ULTRAM) 50 mg tablet
Take 1 tablet (50 mg) by mouth every 6 hours as needed for up to 3 days, Disp-12 tablet, R-0, e-Prescribing, maximum MEDD: 20 mg MEDD for this order

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Best practice advisory

SANF⊇RD imagenetics

Based on this patient's genetics:

Codeine containing products and tramadol are not recommended due risk of toxicity including respiratory depression and death.

⚠ Non-opioid analgesics such as NSAID's and COX2 inhibitors should be considered based on type, severity, and chronicity of pain.

Opioid alternatives include: tapentadol, morphine, fentanyl, hydromorphone and oxymorphone. Opioid alternatives with uncertain toxicity for this patient include hydrocodone and oxycodone.

Reference: Crews, et al. Guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy. December 2020.

Remove the following orders?

Remove	Keep

⌂ Acetaminophen-codeine #2 (TYLENOL #2) 300-15 mg tablet
Take 1 tablet by mouth every 6 hours as needed for up to 3 days, disp-12 tablet, R-0, e-Prescribing, maximum MEDD: 9 mg MEDD for this order

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Figure 1.   Clinical decision support examples.
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implications of *CYP2D6* polymorphisms on these medications to translate into evidence-based guideline therapeutic recommendations. Additionally, the impact of *OPRM1* and *COMT* need to be explored to further define their role. While *CYP2D6* is commonly included in PGx panel testing, *OPRM1* and *COMT* generally are not. Currently, there is no standardization for *OPRM1*, and *COMT* genotype to phenotype association, and most of the platforms that do include *OPRM1* and *COMT* only test *OPRM1* rs1799971 and *COMT* rs4680 [10]. Another genetic consideration is *ABCB1* which encodes for P-glycoprotein and may alter the pharmacokinetics of opioids. The clinical implications are unclear at this point but exist as another target for further research [23].

Some complexities exist with *CYP2D6* when compared with some other CYP450 enzymes. Copy number variants (CNVs) are common with *CYP2D6* [24]. *CYP2D6* CNVs include duplication or deletion and potential rearrangement with *CYP2D7* [25]. Many laboratory tests lack the ability to determine the exact number of CNV present, which can complicate interpretation and cause confusion among providers and patients, particularly if different results are returned from different laboratories upon repeated testing [26]. In some cases, *CYP2D6* results may be reported out as indeterminate when uncertain function alleles are identified. Utilizing PGx to guide opioid prescribing is not nearly as beneficial for patients with such results at this time, but advances in research and technology will hopefully provide a clearer picture of *CYP2D6* analysis in the future.

These and other scientific considerations have led to the development of clinical practice guidelines from the CPIC. Originally published in February 2012 under the name 'Clinical Pharmacogenetic Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of Cytochrome P450 2D6 (CYP2D6) Genotype', these guidelines were further updated in April 2014, April 2017, October 2019, and most recently under a revised name in December 2020 [10]. Future research must continue as implementation work progresses to perpetually revise and strengthen treatment guidelines over time as new evidence emerges.

The need for more studies related to pain and PGx is evidenced by current investigations in the field. A Depression and Opioid Pragmatic Trial in Pharmacogenomics (ADOPT-PGx), is an NIH-funded pragmatic trial examining if available pharmacogenetic data results in better pain control in patients when compared with usual care. The study is enrolling patients with acute post-surgical pain and chronic pain [27]. Medstar Health Research Institute is enrolling patients in its PGx Applied to Chronic Pain Treatment in primary care trial which is an open-label, prospective, randomized trial. Patients on opioid therapy will be randomized to PGx-guided care versus usual care [28]. A search of open clinical trials suggests many related studies also exist. These studies are moving the field forward, however much more research is needed especially looking beyond the role of solely *CYP2D6* in treatment-guided opioid therapy.

Proper utilization of *CYP2D6* information to help guide opioid prescribing should include, among many other variables, consideration of phenoconversion. Medications that are strong CYP2D6 inhibitors can cause a *CYP2D6* normal metabolizer patient to respond as a poor metabolizer (activity score of 0). Moderate CYP2D6 inhibitors also can influence patient response. Currently, PGx-related CDS may not account for potential phenoconversion. Incorporating CYP2D6 inhibitors that a patient is on into an algorithm to provide recommendations will be a crucial step in optimizing PGx opioid CDS.

It is important to note that PGx guidelines alone provide only one variable in the highly complex topic of opioid-driven pain management. More robust opioid selection and dosing algorithms may become more helpful when taking into account PGx as well as many other patient-specific factors. Because pain is subjective, there is potential for more variation of outcomes compared with more quantitatively monitored conditions, such as warfarin/anticoagulation (warfarindosing.org). Even within the context of PGx alone, there are multiple factors to consider related to opioid metabolism. Demographics (age, gender, ethnicity, race), environment, other disease states/conditions and medications and indications for opioid use should be considered. Researching these interwoven issues may help to provide more clarity on opioid optimization. We believe that research must expand to further guide opioid-focused PGx implementation efforts in a data-driven manner.

Clinician education & CDS

The difficulties of clinically implementing PGx have been described for years in a variety of literature sources, with education being regularly referenced as a specific barrier [29,30]. As the science of PGx is newer, many clinicians may not have received education or training in their undergraduate, graduate or residency training experiences. Specifically, some physicians may feel unprepared to use genetic information in their practice [14], with similar findings observed for pharmacists and other healthcare professionals [31,32]. This lack of knowledge continues to be documented in recent literature, despite generally favorable feelings toward PGx [33]. Although it has been ensured

that education and training programs involve PGx in the classroom [34], continuing education materials may be helpful for practicing clinicians with a limited understanding of PGx concepts [30]. Strong examples exist in different settings for healthcare professional education, such as what has been described for the Mayo Clinic, but challenges of broad education remain [35].

One global pharmacy and medical education survey suggests that PGx education has improved in recent years [36]. However, the breadth and depth of PGx training vary across educational programs [37,38] despite the presence of consensus-based pharmacist competencies and guidelines for PGx knowledge attainment and clinical application [39]. Guidelines from the Center for the Advancement of Pharmacy Education and Accreditation Council for Pharmacy Education, continuing education, certificate programs and degree programs are currently being offered to educate practicing pharmacists [39,40].

One method to reduce the breadth and depth of educational needs on the topic is through CDS infrastructure [13]. Active CDS that guides prescribing practices based on genetic data has been noted as a key component of successful implementation [30]. Although interpreting the CDS tools may still require some baseline level of knowledge about PGx, these tools may be one way to facilitate greater engagement without substantial education and may help to overcome educational barriers [41]. Rather than needing to thoroughly understand clinical decisions that should be made in the context of a drug–gene interaction, support tools can provide more specific guidance to the clinician. However, CDS tools have been developed in markedly different ways across different electronic health records, and diversity among them has created difficulty in assessing the effectiveness of interventions [42]. Further, CDS functionality within EHRs has been identified as a barrier to effective CDS integration [43], as has the relative prioritization of PGx CDS [44].

There are several unique demonstration projects that each suggest operationalizing CDS for PGx is viable in a variety of settings [45,46]. The genomic prescribing system is one example of an online, secure, custom interface for PGx CDS that has been operational for several years, which leverages color-coded indicators of PGx risk for ease of understanding [47]. In the first 43 months since inception of the genomic prescribing system program, 100% of red lights were clicked, 79% of yellow lights were clicked and 43% of green lights were clicked, demonstrating strong and sustained utilization by a variety of clinicians. Even sites with limited EHR infrastructure solutions have been suggested to support CDS [48]. Further, publications that highlight strategies for effective CDS integration have been published in recent years that can provide guidance to organizations that are looking to add CDS [47,49–51].

To be most useful, CDS technologies must take into account several clinical variables. As pain management is inherently complex and patient-specific, it is difficult to assemble a comprehensive CDS tool. However, the PGx complexities of opioid management are largely straightforward due to their focus on *CYP2D6* polymorphisms at this time. Therefore, PGx-focused CDS for pain management may be appropriate as a confirmatory step after the provider or team has identified a preferred pain management strategy. It may also be appropriate to consider related drug–drug interactions and phenoconversion at this confirmatory stage as well. However, drug–drug interactions within the context of opioid use should not be a novel consideration. Provider-focused educational efforts are still important when CDS is involved [52], but less education may be required to more narrowly support pharmacogenetics of opioid use when CDS is already in place. Given the relatively specific and limited necessary guidance, CDS tools for opioid use may offer more viable implementation. Consistent clinical consults have similarly been described as a pathway toward PGx-optimized opioid use [53].

Just as no clinician is expected to be a profound expert of every content area in the field of medicine, it may be more practical for most clinicians to possess a more minimal level of competence and fluency with PGx as a broad science, while a smaller set of specialists take on the role of specific content-level expert [34]. Similar to other specialty services, PGx consult services have demonstrated utility in the hospital setting [54]. Referrals to ambulatory clinics also exist in similar ways [12,16,50,55]. These approaches may be beneficial when the front-line provider is not finding success in pain management and when PGx is a suspected contributing factor. We believe that basic and general PGx knowledge is necessary for all clinicians, that CDS is not a substitute for education, and that PGx specialists should be identified and available to assist with complex PGx decisions.

Economic, health policy & public health considerations

Widespread implementation of PGx use in clinical decision making, as with all healthcare practices, requires evidence of both clinical and economic benefits. Specifically related to economic considerations, the implementation of PGx treatment algorithms must be justified by virtue of cost savings for health payers and to the healthcare system as a whole. The general economic and societal cost of opioid misuse is well-documented [56]. In recognition of this,

payers may consider reimbursement incentives to support the evaluation of a patient's relevant PGx data prior to initiating outpatient opioid treatment as a way to better ensure therapeutic optimization.

Recent increases in the prescribing of codeine and tramadol creates both concern and opportunity for intervention [57,58], as codeine and tramadol are two agents with some of the strongest evidence for PGx-guided therapeutic optimization [10]. There may be an opportunity to provide prior authorization criteria to enforce the administration of PGx testing and the documentation of a CYP2D6 activity score, which could support the selection of alternate agents in the case of *CYP2D6* poor or ultra-rapid metabolizers. As the evidence evolves over time, as PGx testing results become more broadly available, and as the cost of PGx testing continues to decrease, prior authorization criteria could be adjusted accordingly. Balancing pharmacoeconomic considerations with health outcomes is difficult but necessary in a healthcare environment with scarce resources.

It is important to clarify that the implementation of prior authorization criteria should not be done in such a way as to further limit or delay the critical access to necessary pain medications, but as a way to support engagement of PGx testing in appropriate circumstances. For instance, prospective PGx testing could be ordered prior to elective surgeries or other situations where opioid needs could be reasonably anticipated. When such foresight is impractical, a prior authorization could serve as a warning that prescribing beyond an initial quantity may require PGx testing to better ensure a beneficial safety and efficacy balance exists for the patient. Similarly, to reduce impediments to opioid access, systems must be in place to support a robust and easy-to-access, yet secure, framework which allows each patient's PGx data available. The use of systems such as prescription drug monitoring programs has been discussed as one potential way to document and store a patient's relevant PGx phenotypes and make them available at the point of prescribing or dispensing [59]. Expanded integration of EHRs both between health-systems and outpatient pharmacies, or the implementation of other data sharing strategies would be substantially beneficial in ensuring continuity of PGx-guided decision making for patients across healthcare settings.

Availability of PGx information at the point of dispensing for community pharmacists, coupled with expansion in the scope of practice to allow for therapeutic substitution, may reduce or eliminate delays that may arise through a prior authorization-based process. In lieu of scope expansion, implementation of collaborative agreements between physicians and pharmacists that allow pharmacists to make substitutions in accordance with prior authorization criteria could reduce delays at the point of dispensing. However, a collaborative practice may be less effective in implementation, as multiple collaborative agreements may need to be in place to allow for therapeutic substitution across their entire patient population. Efforts should be made to advance health policy in such a way that empowers healthcare professionals to ensure opioid optimization has taken place while mitigating safety issues and supporting efficacy.

Implementation of prior authorization criteria would necessitate patient and provider access to PGx phenotypes. As testing costs decline over time and as more patients have either direct-to-consumer or provider-ordered PGx information on file, the lack of PGx data may diminish over time. However, PGx testing coverage and other related economic variables may create a foundational barrier to the relatively limited number of patients who currently receive PGx testing. This may be corrected by adopting public health recommendations that encourage preemptive PGx testing for patients, similar to existing guidelines for preventative health screenings and vaccinations. Proactive PGx testing may be more easily justified from a cost perspective, as a patient's genetic information will not change over time, and if results are obtained early and are accessible, the cost of the test is theoretically spread across multiple pharmacotherapeutic decisions that span a patient's entire life. The use of a robust data storage and sharing system, as described above, would limit (or ideally, eliminate) the need for repeat genetic testing and optimize the cost–effectiveness for the testing procedure. We believe that continued economic analyses will help to guide policy decisions for PGx implementation and that existing PGx data must be shared among healthcare professionals to ensure that previously obtained PGx information is not wasted but is used to optimize patient care.

Ethical clarity & consensus

PGx is an area of medicine replete with complex ethical, social, and legal concerns. Some of these complicated issues include the implications of the high-cost therapeutics and the inequitable access to them; ownership of genetic information and how it is obtained, stored, and used; and potential discrimination and social justice ramifications of genetic-based stratification of patients [60]. But lacking widely accepted explicit professional and ethical norms, attempts to merely balance costs/benefits seem ill-suited to address the wide-ranging PGx related moral issues.

Novel therapeutics and diagnostics entail novel and potentially astronomical research and development costs, irrespective of potential efficacy. The cost of development, as well as the search for return on investment, may lead to

unintentional but foreseeable disparities in access to potentially life-saving therapeutics. Historically disadvantaged communities will be the most adversely impacted by limited access to novel therapies, particularly genetic-based therapies. While the overall cost of genetic testing has declined in recent years, direct test costs, insurance coverage, and co-pays still represent additional substantial barriers to equitable access to PGx on top of existing structural and systemic healthcare disparities.

Ownership of genetic data is also a serious, long-standing concern [61]. Certain specific protections against unconsented, harmful genetic information disclosure exist, including the Genetic Information Nondiscrimination Act [62] and the Patient Protection and Affordable Care Act [63]. These protections should, theoretically, shield patients and research participants and encourage wider acceptance. However, serious concerns persist, specifically regarding disclosures that adversely impact the patient in unexpected ways [64–66].

Consider the following example: a primary care provider is considering sending a patient's sample to an outside laboratory for genetic analysis with the hope of developing a targeted, individualized treatment plan. Of the four laboratories available for this genetic analysis, each has very different approaches to handling the patent's genetic data. Neither Laboratory 1 or 2 permit nor make accommodations for individual patients to opt-out of their samples being used in subsequent research, either by the laboratory or, as is more often the case, by third-party researchers. Laboratories 1 and 2 operate under an ethically tenuous implied consent approach to subsequent research; they presume that when samples are sent in for genetic analysis, then consent for any subsequent research activities is provided. Laboratory 3 allows for patients to opt-out of subsequent genetic testing. Still, the process is arduous on the patient, and the process is only detailed in the fine print of the sample submission process, which the patient may or may not have access to before the sample is submitted. Thus, while an opt-out process is beneficial to the patient's ability to control their data, the burden of exercising this benefit is disproportionately on the clinician who obtains informed consent from the patient and on the patient herself. At last, Laboratory 4 takes a very different approach to issues of consent for research. Laboratory 4 provides documents and training for clinicians to utilize when gaining informed consent from the patient, which includes details about future research participation and the ability to opt-out without adverse consequences to the patient.

Many additional questions exist related to data ownership and research. For instance, who owns the data yielded from genetic tests? Does the patient have the opportunity to remove their data from research projects or business activities? Are patients owed compensation if their data results in financial windfall? Should an individual have the opportunity to monetize their genetic data? No current consensus exists on these questions, but answering these questions may help with confidence in PGx, specifically if the target patient population is historically underserved or marginalized.

Finally, many are concerned that the categorization and sub-categorization of groups of people intrinsic to the clinical application of PGx may further exacerbate existing social inequalities and discrimination. Shields worried about the framing of PGx data in relation to race. Framing new PGx data 'in terms of 'racial differences' in allele frequencies relevant to disease risk or drug response continue[s] a long and painful history of comparative racial science in the US' [67]. The intersection of amorphous psychosocial categories and 'socially charged phenotypes' may result in unanticipated, socially problematic consequences that have the potential to outstrip the expected benefits of PGx.

Although conceptually straightforward and widely employed in public health ethical analyses, a utilitarian cost-benefit approach falters in the face of multifaceted intersections of ethical ambiguity. PGx requires more normative sophistication precisely because of the intersectionality of patients whom PGx intends to benefit. We believe that addressing the resilient, morally ambiguous concerns associated with personalized medicine and PGx will require persistent dialogue between professionals and within professions.

Conclusion & future perspective

Areas of advancement needed for more robust pharmacogenomic engagement include clinical and economic research needs, education and training needs, policy and public health considerations and legal and ethical issues. Leaning on published models of implementation successes may help to facilitate the expansion of PGx-driven opioid optimization. While PGx represents only one variable in the highly complex field of pain management, continuing efforts to address these issues may help to further operationalize PGx as a strategy for improving opioid use. Further research on the role of pharmacogenomic guidance within the opioid management process, advances in PGx education, and the development of health policy and responsible data sharing will help to clarify next steps in PGx-focused opioid optimization to improve pain management.

Executive summary

Opioid misuse is a public health crisis with troubling trends & statistics

- The US Department of Health & Human Services Response to the Opioid Crisis includes five points, one of which is to advance the practice of pain management enabling access to high-quality, evidence-based pain care.
- Clinical guidelines from the Clinical Pharmacogenetics Implementation Consortium have been recently updated and include guidance related to the intersection of pharmacogenomics (PGx) and opioid use.
- Barriers remain to widespread implementation of PGx within the context of opioid management.
- Emerging practice models exist in hospitals, ambulatory care and community pharmacies where PGx-informed pain management is practiced.
- Existence of emerging practice models with associated replication in different healthcare environments implies that there is potential for PGx guidance to positively impact opioid selection in many settings.

Ongoing research, education & clinical decision support

- Current research and practice guidelines suggest strongest levels of evidence for therapeutic recommendations for *CYP2D6* with codeine and tramadol.
- Additional trials are ongoing to explore PGx-guided opioid management improves outcomes as compared with usual care.
- Though strong examples of PGx-focused education for healthcare professionals exist, broad education across health professions is inconsistent.
- Clinical decision support (CDS) tools may help to guide clinicians as PGx is implemented. However, as pain management is highly complex, creation of a comprehensive CDS tool is difficult.

Economic, health policy, public health & ethical/legal considerations

- Costs associated with opioid use and misuse are problematic, and balancing pharmacoeconomic considerations with health outcomes is difficult but necessary.
- PGx data sharing is necessary to ensure that previously obtained PGx information is not wasted.
- Continued economic analyses may help to guide policy decisions for PGx implementation.
- Disclosure issues surrounding PGx data should be carefully balanced to ensure appropriate access without misuse.

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