Editorial

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Pharmacogenomics

Application of pharmacogenomics in supportive oncology: a patient journey

Dung G Nguyen[1], Sarah A Morris[1] & Jai N Patel*,[1]

[1]Department of Cancer Pharmacology & Pharmacogenomics,Levine Cancer Institute, Atrium Health, 1021 Morehead Medical Drive, Charlotte, NC 28204, USA

*Author for correspondence: Tel.: +1 980 442 4113; jai.patel@atriumhealth.org

"Although the impact of PGx on drug pharmacology can be extrapolated to virtually any patient population, it is important that evidence-based data and implementation science continue to drive the field of medicine rather than empirical data alone"

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Pharmacogenomics in supportive oncology

Cancer-related symptoms, including depression, anxiety, nausea, vomiting and pain, negatively impact functional status and quality of life in patients with cancer. Pain occurs in approximately two-thirds of patients with cancer, with over one-third experiencing moderate to severe pain [1]. Depression affects up to a quarter of patients, especially in the first year after diagnosis and during treatment [2]. Early management of cancer-related symptoms improves quality of life, treatment adherence and, possibly, survival [3]. Nonetheless, effective management of these symptoms remains a challenge because of interindividual variability in response to supportive care medications, which can be partly attributed to genetic variations affecting drug pharmacology. Personalized supportive care treatment using genetics is one strategy for moving away from the traditional trial-and-error approach.

Pharmacogenomics (PGx) studies the impact of genetic variations on drug response. Data suggest that 99% of patients carry at least one clinically actionable PGx variant for which guidelines are available [4,5]. The US FDA Table of Pharmacogenetic Associations and peer-reviewed clinical guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) provide guidance on translating PGx results into actionable prescribing decisions for many drugs, including opioids, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants and antiemetics [6–8]. For example, CYP2D6 poor and ultrarapid metabolizers are at risk of either inadequate analgesia or toxicity with certain opioids, particularly codeine and tramadol, but also, to a lesser degree, hydrocodone [9]. Limited evidence also suggests the impact of *COMT* and *OPRM1* on opioid sensitivity. NSAIDs are metabolized by *CYP2C9*, genetic variations of which have been linked to increased drug exposure and toxicity risk [10]. Selective serotonin reuptake inhibitor and tricyclic antidepressant response and toxicity can be affected by genetic variations in *CYP2C19* and *CYP2D6*, with emerging evidence suggesting the role of *SLC6A4* and *HTR2A* polymorphisms, though further research is needed [11,12]. In this editorial, the authors highlight how PGx can be applied to supportive oncology treatment through a theoretical patient journey.

The oncology patient journey

Initial work-up

As a patient establishes care at a cancer center, initial work-up consists of disease screening, risk assessment and clinical testing, including labs, imaging and biopsy. The National Comprehensive Cancer Network recommends distress screening at the initial visit, periodically and as clinically indicated to help identify symptoms that may prompt supportive oncology interventions [13].

Multigene preemptive PGx testing can be performed with the initial work-up to help guide selection and management of medications at the time of testing and downstream. If testing all patients is not feasible, cancer

centers could consider prioritizing testing in patients at high risk of cancer-related symptoms as determined by early distress screening. High-risk patients may also include those currently prescribed or considering medications with FDA or CPIC PGx guidance or presenting with specific cancer-related symptoms, such as pain or depression. Pretest interruptive alerts can also help identify patients being prescribed high-risk medications with PGx guidance and prompt PGx testing.

Blood, buccal or saliva samples are collected at the initial visit. Buccal and saliva are noninvasive and can be stored at room temperature, and collection kits can be mailed to patients for self-collection. Integrating one additional sample collection for PGx testing with the initial work-up can inform prescribing for over 30 supportive care-related medications with CPIC and/or FDA guidance.

Patient case

SO is a 66-year-old woman presenting at her initial oncology visit for evaluation of changes in bowel habits and unexpected weight loss. Distress screening is notable for a pain score of 8/10 and Patient Health Questionnaire 2 score of 3/6 (suggesting possible major depressive disorder). Patient provides buccal swabs in clinic for PGx testing.

Clinical laboratory processing

Genotyping is performed at an in-house or commercial Clinical Laboratory Improvement Amendments-certified laboratory. The test should include key pharmacogenes with FDA or CPIC PGx guidance related to supportive care medications (e.g., *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6* and *CYP3A5*) and chemotherapies (e.g., *DPYD*, *UGT1A1* and *TPMT*/*NUDT15*). The Association for Molecular Pathology PGx working group has published recommendations to standardize inclusion of clinically relevant alleles in PGx assays [14]. CPIC and Pharmacogenomics Knowledge Base have developed translation tables to standardize genotype-to-phenotype reporting, and CPIC guidelines can guide translation of PGx results into prescribing actions, which can be integrated into the electronic medical record (EMR) as clinical decision support. Commercial platforms are available to provide PGx translational services, though careful consideration should be taken as to whether CPIC translation and reporting standardization is followed.

Diagnosis & treatment decisions

Similar to other labs, discrete PGx results are uploaded and stored in the EMR. Patient-specific actionable PGx results trigger post-test alerts for providers to consider an alternative medication or dose modification at the time of prescribing. These alerts and accompanying functionality should be strategically integrated into providers' clinical workflow to minimize alert fatigue.

Clinical pharmacists are uniquely positioned to provide PGx consultation services. Pharmacists interpret PGx results and communicate recommendations to providers. Importantly, PGx information should always be considered along with other clinical factors, such as drug–disease interactions, drug–drug interactions and phenoconversion, a phenomenon in which a drug may alter the patient's phenotypic metabolizing status. PGx results and educational materials are accessible to the patient through a patient portal, and a pharmacist is available to counsel patients.

Patient case (continued)

SO will start adjuvant chemotherapy for stage III colon cancer. PGx results are notable for CYP2D6 ultrarapid metabolizer (*1/*2 × 2) and CYP2C19 rapid metabolizer (*1/*17). When the oncologist orders ondansetron for chemotherapy-induced nausea/vomiting prophylaxis, the post-test alert notifies the prescriber of the patient's risk of decreased response and to use an alternative agent not predominantly metabolized by CYP2D6, such as granisetron. The palliative medicine provider orders tramadol, and the post-test alert suggests to avoid tramadol because of the potential for toxicity in CYP2D6 ultrarapid metabolizers and to consider an opioid not extensively metabolized by CYP2D6, such as morphine or hydromorphone.

Treatment monitoring & follow-up

As changes are made to the patient's medication profile during the cancer care continuum, PGx results and post-test alerts remain in the EMR as valuable tools for prescribing. PGx information can also be utilized by non-oncology providers caring for the patient (e.g., the patient's CYP2C19 rapid metabolizer status may be informative for antifungal management with voriconazole by the infectious disease provider). Additionally, pharmacist-driven PGx consultation services (available electronically in the EMR) are available to support prescribers in interpreting results.

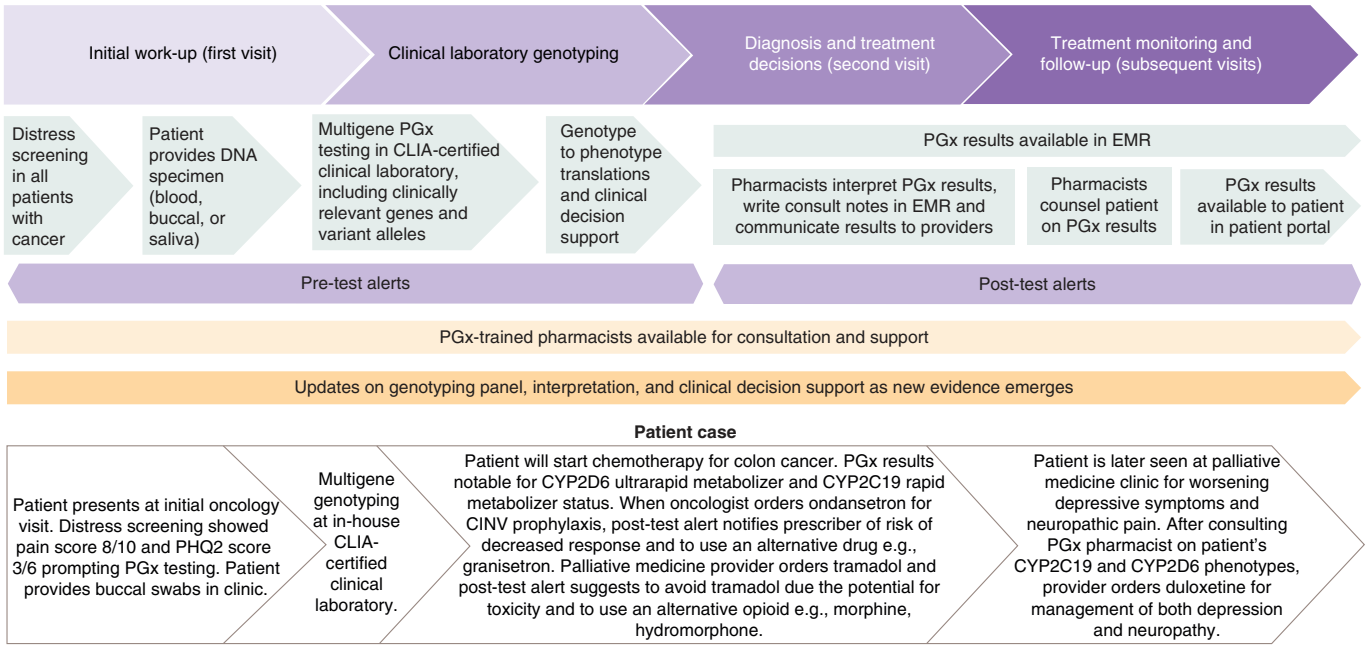

Figure 1. Potential value of pharmacogenomics through an oncology patient journey.
CINV: Chemotherapy-induced nausea and vomiting; CLIA: Clinical laboratory improvement amendments; EMR: Electronic medical record; PGx: Pharmacogenomics; PHQ2: Patient health questionnaire 2.

As more evidence emerges and more guidelines are published, it is important to update result interpretations and clinical decision support tools. Institutions are encouraged to stay current with PGx updates from the FDA, CPIC, Pharmacogenomics Knowledge Base, Pharmacogene Variation Consortium and Association for Molecular Pathology.

Patient case (continued)

SO is later seen at the palliative medicine clinic due to worsening depressive symptoms and neuropathic pain from oxaliplatin. Based on the patient's CYP2C19 and CYP2D6 phenotypes, she may be at increased risk of therapy failure with several selective serotonin reuptake inhibitors, including citalopram, escitalopram and paroxetine. After consulting the PGx pharmacist, the provider orders duloxetine for the management of both depression and neuropathy (Figure 1).

Current state of evidence

Although there is an abundance of data suggesting that PGx affects pharmacokinetics and response to several medications prescribed for cancer symptom management, there are limited studies of PGx in supportive oncology. In a retrospective study of nearly 7000 adult patients with cancer undergoing distress screening, approximately half reported a considerable symptom burden that was significantly correlated with prescribing of symptom control medications [15]. It was estimated that at least one-quarter of these patients would carry an actionable genotype that was informative for symptom control prescribing. Another retrospective analysis in over 60,000 adult patients with cancer found that over half received multiple opioids [16]. In the *CYP2D6* genotype cohort of 105 patients, CYP2D6 intermediate and poor metabolizers were over fivefold more likely to experience pain-related hospital encounters compared with normal and ultrarapid metabolizers. A small prospective study in a palliative oncology clinic found that patients with actionable genotypes receiving PGx-guided pain management had the highest rate of pain improvement [17]. Finally, in a single-arm pilot study of patients with cancer and uncontrolled pain, pain improvement was significantly greater with PGx-guided pain management compared with historical data [18].

A few ongoing trials are studying the impact of PGx in supportive oncology. An observational prospective study at the Mayo Clinic aims to evaluate patient perceptions of their quality of life and provider perspectives on the clinical utility of PGx testing in optimizing supportive care medications in stage III–IV cancers (NCT04067960). Two prospective interventional trials at the Levine Cancer Institute are studying the benefit of PGx-guided

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supportive oncology management across two populations: patients with cancer referred to palliative medicine and those undergoing hematopoietic cell transplantation (NCT04500301 and NCT04727827, respectively) [19]. Finally, a pragmatic randomized trial at the University of Florida is examining whether *CYP2D6* genotype-guided opioid treatment results in improvements in pain and symptom severity and daily living quality compared with conventional prescribing in patients with metastatic solid tumors and pain score ≥4/10 (NCT02664350) [20].

Despite some randomized trials of PGx in the general population, there is limited understanding of the generalizability of these findings to cancer populations and a lack of large prospective trials in supportive oncology. Although the impact of PGx on drug pharmacology can be extrapolated to virtually any patient population, it is important that evidence-based data and implementation science continue to drive the field of medicine rather than empirical data alone.

Author contributions

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