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ISMP Medication Safety Alert!®
Educating the Healthcare Community About Safe Medication Practices

Utilizing pharmacogenomic testing can improve medication safety and prevent harm

Problem: Genetic variations have been used to identify the potential for disease, but the impact of genetic variations on an individual's response to medications, referred to as pharmacogenomics (PGx), is not yet as widely used. In our 2021 newsletter article, *Screening for dihydropyrimidine dehydrogenase (DPD) deficiency in fluorouracil patients: Why not?* (www.ismp.org/node/25770), we shared how saddened we were to learn about a patient's death that may have been prevented if DPD deficiency testing had been completed prior to starting fluorouracil. Having this information beforehand allows prescribers to preemptively reduce the dose of the patient's medication and mitigate potential toxicities, or avoid the therapy if the patient has DPD deficiency. Since then, we have received additional reports of patient deaths from the lack of screening for DPD activity prior to initiation of fluoropyrimidines (i.e., fluorouracil, capecitabine). In reviewing the literature surrounding the hesitancy to adopt universal screening, the risk of patient harm and potential fatality seems clear, and the hurdles to implement widespread testing seem to be manageable. Our position in support of DPD testing remains the same.

Furthermore, in 2022, the US Food and Drug Administration (FDA) approved updated prescribing information for **XELODA** (capecitabine) (www.ismp.org/ext/1316) to warn about serious, including fatal, adverse drug reactions (ADRs) from DPD deficiency, and recommends that prescribers discuss with patients whether they should be evaluated for genetic variants associated with this risk. Just recently, in March 2024, FDA approved similar labeling changes for fluorouracil injection products (www.ismp.org/ext/1355). In 2022, one organization, Dana Farber, implemented a reminder-based PGx testing program for patients prior to receiving fluoropyrimidines, achieving a testing rate of 90%. During the first 10 months, the program screened 1,043 patients and was able to identify 43 at-risk patients who were evaluated for preemptive dose reductions.[1]

Since our article was published, the integration of pharmacogenetic testing into clinical practice for several medications has become more widespread, aiming to prevent ADRs, optimize dosing, and enhance patient safety.[2] However, not all healthcare practitioners and organizations are aware of the vast array of medications that have testing recommendations, or the potential for patient harm if it is not done. While testing is mostly covered by insurance, this varies from state to state, as does cost-effectiveness, which varies by organization depending on volume and laboratory test availability. Other challenges include test result turnaround time (e.g., 3 days for in-house versus 5 to 10 days if using an external laboratory), laboratory variability in the comprehensiveness of genotype testing, difficulty interpreting test results, and a lack of knowledge regarding adjustment of drug doses based on the results. Consequently, practitioners may lack expertise on how to implement a PGx program to prevent medication-related harm in their organization.

For this reason, we sought insights and best practices for incorporating PGx into clinical care from experts in the field. Practitioners at South Florida's Nicklaus Children's Hospital (previously known as Miami Children's Hospital) have pioneered personalized medicine for pediatric care, offering insights and best practices for integrating PGx testing to enhance medication efficacy and reduce ADRs.[3] Their innovative PGx program is at the forefront of precision medicine and is described below.

continued on page 2 — Pharmacogenomic testing >

SAFETY briefs

Errors when converting between salt and elemental dosages. A pharmacist recently reported an error involving a patient who was taking potassium gluconate 595 mg by mouth twice a day at home. When the patient was hospitalized, the home medication was continued in error using elemental potassium 99 mg tablets. This transcribing error, at the point of medication reconciliation, required the patient to take 6 elemental potassium 99 mg tablets at once. Some manufacturers label oral potassium products in terms of the salt (in this case, potassium gluconate 595 mg), while others indicate the amount of elemental potassium (99 mg) (**Figure 1**, page 2). There may or may not be cross-referencing of the conversion on the principal display panel and other aspects of label display panels. Also, when pharmacists enter a patient's home medication list in their electronic health record (EHR), medications that are continued are selected from a list supplied by one of the drug information vendors. In this hospital, when potassium gluconate was continued, it appeared in the EHR for verification but mapped it to a 99 mg elemental potassium tablet, not the salt. Since the order was for 595 mg, the system assumed the dose should be 6 tablets. Each potassium gluconate 595 mg tablet contains 99 mg

continued on page 2 — SAFETY briefs >

> Pharmacogenomic testing — continued from page 1

Pharmacogenomic Program Overview

The PGx program at Nicklaus Children's Hospital provides personalized treatment plans for various conditions, including behavioral health issues, oncology, pain management, and infectious diseases. The program is founded on three pillars: an extensive PGx test panel, available in-house; advanced clinical decision support (CDS) systems integrated with electronic health records (EHRs); and a team of PGx experts committed to supporting practitioners and educating patients about PGx test results.

PGx testing can be both reactive and preemptive. Reactive testing occurs when a medication has already been prescribed and involves genes known to influence the drug's efficacy. In contrast, preemptive testing is conducted before any medication is needed, allowing for the anticipation of potential genetic interactions with future treatments. The program at Nicklaus Children's Hospital focuses on preemptive PGx care, and results are stored within the EHR for future reference.

Current Guidelines

The Clinical Pharmacogenetics Implementation Consortium (CPIC), supported by the National Institutes of Health (NIH), is an international consortium whose interest is facilitating the use of PGx tests for patient care. The group has been instrumental in providing recommendations for dose adjustments, identifying medication hypersensitivity risks, and has developed more than 26 guidelines for 25 genes relevant to 90 drugs,[4] including for fluoropyrimidines based on dihydropyrimidine dehydrogenase genotype (www.ismp.org/ext/1352). In addition, the FDA-approved labels for these adult and pediatric medications now include PGx-based dosing recommendations and hypersensitivity risk assessments, highlighting the critical role of PGx in enhancing medication safety.[5]

Impact of Testing

At Nicklaus Children's Hospital, PGx test results are used to assess the activity of enzymes, which play a vital role in the metabolism of many medications. The expansive PGx testing panel includes screening for gene variants to preemptively identify patients at risk of DPD deficiency. This proactive approach enables tailored dosage adjustments, significantly mitigating the risk of severe drug-induced toxicity.

When it comes to medications used in behavioral health, genetic variation in drug metabolizing enzymes cytochrome P450 (CYPs) CYP2D6, CYP2C19, and CYP2B6 can affect how several antidepressants are metabolized, potentially influencing their dosing, effectiveness, and side effect profile. Practitioners use this information to determine appropriate dosing and drug selection.[6] To cite another example, the metabolism of most proton pump inhibitors is influenced by the CYP2C19 enzyme, with variations in the CYP2C19 genotype affecting medication exposure, effectiveness, and side effects. Practitioners can tailor proton pump inhibitor therapy using the patient's PGx profile.[7]

In more critical cases, PGx results related to CYP2C9 and/or vitamin K epoxide reductase complex subunit 1 (VKORC1) genes can predict high sensitivity to warfarin, where standard doses may increase bleeding risks.[8] Additionally, alterations in the thiopurine methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15) genes can lead to the accumulation of harmful metabolites, increasing toxicity risks with standard thiopurine medication doses. Preemptive genetic testing for TPMT and NUDT15 is a recognized protocol across numerous institutions, guiding thiopurine treatment.[9]

These examples highlight the impact of PGx testing implementation on medication safety.

continued on page 3 — Pharmacogenomic testing >

>SAFETY briefs continued from page 1

of elemental potassium, thus, 6 elemental potassium 99 mg tablets results in a six-fold overdose. The patient erroneously received the higher dose for a few days; fortunately, the patient was not harmed.

Figure 1. Inconsistent dietary supplement labeling of potassium based on the salt (left), or the elemental content (right) led to a medication error.

Similar confusion exists with most oral iron products, as well as zinc, calcium, and magnesium, all of which are regulated as dietary supplements by the US Food and Drug Administration (FDA), not drugs. For example, in our February 8, 2018 newsletter, we wrote about a patient who was receiving 5 tablets of ferrous sulfate daily, to equal the 325 mg dose recommended by the patient's physician. The ferrous sulfate purchased at a pharmacy was only labeled with the amount of elemental iron in each tablet, 65 mg. The carton's principal display panel provided no indication that each tablet was equivalent to the salt form of ferrous sulfate 325 mg. The patient experienced severe constipation and stopped taking the iron after 2 days but was soon hospitalized for other reasons, where the error was discovered.

The longstanding lack of standardization of dietary supplement labeling has led to frequent dispensing and administration errors. Many products express the salt form on the principal display panel but print the elemental form in the label's Supplement Facts panel, which may be overlooked. Labeling of these oral supplements consistently in terms of both the quantity of the active moiety (e.g., elemental amount in mg of potassium, iron, zinc, magnesium) as well as the mg of salt (e.g., potassium gluconate, iron sulfate), would reduce

continued on page 3 — SAFETY briefs >

> Pharmacogenomic testing — continued from page 2

Safe Practice Recommendations: We encourage organizations to evaluate the feasibility of implementing a PGx program and consider the following recommendations:

Designate a team and gather resources. Review your organization's position on PGx testing and assess the need for establishing, modifying, and/or expanding services. Review the CPIC guidelines,[4] prescribing information, and published literature to identify medications on your organization's formulary that have associated PGx tests. To better understand what tests and precision therapies are backed by clinical evidence, refer to ECRI's *Genetic Test Assessment* membership website (www.ecri.org/solutions/genetic-test-assessment).

Evaluate medications with available guidelines. Complete a gap analysis by comparing available PGx guidelines versus your organization's current testing status to develop and prioritize a list of medications for testing. Incorporate this as part of the review process when new drugs are evaluated for formulary addition.

Develop organizational guidelines. Guidelines will be needed to identify patients who should be screened with PGx testing based on the established list of medications and/or other patient risk factors. Include resources and guidelines on how to interpret test results. If a genetic variant is detected that requires a medication to be withheld or dose adjusted, include this information in the guidelines. Review and update the guidelines at least annually or sooner based on data (e.g., change in CPIC Guidelines, new test becomes available).

Build guidelines into the EHR. Incorporate the guidelines in the EHR to notify prescribers of the recommended PGx test before ordering medication from the established list (e.g., if a prescriber enters an order for fluorouracil or capecitabine, an alert is generated with the recommended DPD testing prior to initiation).

Choose a laboratory. Meet with laboratory leadership to determine if it is feasible to develop an in-house PGx test or select an external laboratory. Consider turnaround time which may be reduced if in-house testing is used.

Ensure standardized testing. Follow best practices set by the Association for Molecular Pathology (AMP), including incorporating a fundamental set of genetic variants in the genotyping assay.[10] Adhering to these standards ensures the clinical validity of PGx testing, thereby enhancing personalized and effective patient care.

Implement or expand testing. Strive to implement a comprehensive PGx panel covering genetic variants with established clinical guidelines or relevance in targeted medical areas. This comprehensive approach ensures the test results' applicability for an array of different conditions and serves the patient throughout the continuum of care. Develop a means to track patients so that the team will know that their initiative has reliably reached the right patients.

Determine preemptive testing. When feasible, conduct preemptive PGx testing prior to initiating the applicable medication.

Leverage CDS. Integrate PGx testing results along with CDS (e.g., alert for contraindication, dose adjustment) into the EHR. This ensures that practitioners have instant access to essential PGx information, significantly enhancing the clinical decision-making process.

Educate practitioners. Provide practitioners who will be involved with ordering and evaluating PGx test results with a competency assessment to complete during orientation and at least annually thereafter. Educate staff, for example during grand rounds, about your organization's guidelines and how to interpret test results and adjust the dose, when needed.

continued on page 4 — Pharmacogenomic testing >

>SAFETY briefs

continued from page 2

confusion. As such, we have interacted with both FDA CFSAN (Center for Food Safety and Applied Nutrition) and USP.

The hospital reported they plan to change their EHR inpatient build to fix such conversions. USP, FDA, and drug information vendors can help by listing the strengths of these products as both the elemental and salt forms (e.g., potassium 99 mg [as potassium gluconate 595 mg]).

Spike separating from the port of WG Critical Care infusion bags. ISMP has received reports in which an intravenous (IV) administration set spike has spontaneously separated from the infusion port during the administration of a WG Critical Care infusion bag. Most reports have involved norepinephrine 4 mg/250 mL and 16 mg/250 mL, but one organization reported a similar issue with the norepinephrine 8 mg/250 mL infusion bag. If the spike separates from the bag during administration, this could lead to an interruption, inadequate flow, or delay in the medication infusion, resulting in a patient receiving an incorrect dose.

We have notified the US Food and Drug Administration (FDA) and WG Critical Care of this concern. Organizations should consider using an alternative product, if possible. Our safety partner and affiliate, ECRI, has released a hazard alert (www.ismp.org/ext/1351) with recommendations to reduce this risk. If WG Critical Care norepinephrine injection bags must be used, WG Critical Care suggests the following: place the infusion bag on a flat surface to spike; do not spike the IV bag while it is hanging. In addition, do not squeeze the infusion bag while inserting the spike; only grasp the bag by the port while inserting the spike. Verify that the spike is fully inserted into the bag's port so that the spike shoulder is flush with the port. A twisting action may be necessary but do not overtwist. IV bags are single-use only and should be spiked one time. Do not re-enter the same bag more than once.

WG Critical Care told us that norepinephrine bag port design enhancements have been

continued on page 4 — SAFETY briefs >

> Pharmacogenomic testing — continued from page 3

Educate patients. Review PGx test results with patients and educate them about genetic variations that may impact their medication regimen. Provide them with documentation of the test results and encourage them to share this information with practitioners at applicable care settings (e.g., primary care provider, hospital admission, pharmacy) as part of their medication history.

Conclusion

The growing adoption of PGx testing that follows established guidelines for drug-gene pairs is increasingly recognized as an important method for tailoring medication choices and dosages, enhancing patient safety and treatment efficacy. ADR avoidance is an additional incentive that can support the return on investment. Insights and recommended practices from PGx professionals at Nicklaus Children's Hospital stress the importance of **test standardization**, **compliance with clinical guidelines**, and **seamless integration into EHRs** as key safety components for effectively integrating PGx testing into clinical care. ISMP supports this shift toward a more personalized approach to preventing ADRs and patient harm. We encourage standard-setting organizations to consider including PGx in their recommended treatment guidelines.

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Patient received Myxredlin instead of Cardene IV

A patient was admitted to an inpatient unit from the emergency department (ED) on a **CARDENE IV** (ni**CAR**dipine) 40 mg/200 mL infusion. While settling the patient, the nurse was notified that she urgently needed to assist another patient. In anticipation that the newly admitted patient's Cardene infusion was going to run out, the nurse removed what she thought was a carton containing a Cardene bag from the automated dispensing cabinet (ADC). Then, before leaving to care for the other patient, she replaced the Cardene bag that was already infusing with the bag obtained from

continued on page 5 — Myxredlin >

>SAFETY briefs

continued from page 3

made to accommodate variability in IV administration sets and spiking techniques. The port membrane was repositioned to ensure full insertion of the IV administration spike set, and the interior was narrowed and tapered to create a tighter spike connection. Norepinephrine bags with the enhanced port are expected to be available in the second (4 mg/250 mL) and third (16 mg/250 mL) quarters of 2024.

In the meantime, do not use infusion bags/IV administration sets that leak. If you identify a leak, return the bag and IV administration set to WG Critical Care. If spikes are disconnecting from the infusion bags, report the problem to WG Critical Care Medical Affairs (1-866-562-4708), ISMP, and ECRI.

Close call as a result of three-letter character search. A prescriber was searching for **NEO-SYNEPHRINE** (trying to order phenylephrine injection), an alpha-adrenergic agonist used to treat hypotension. The prescriber typed "neo" into the search field in the electronic health record (EHR) and inadvertently selected an order sentence for neostigmine 3 mg intravenously (IV) and ordered it for the patient. During order verification, the pharmacist did not see an indication on the patient's profile for neostigmine, which most often is used for the reversal of nondepolarizing neuromuscular blockade. The pharmacist contacted the prescriber who stated he intended to order phenylephrine 300 mcg IV.

If only a portion of the name is used to search for products or populate fields in the EHR, consider the entry of a minimum of the first 5 letters of the drug name. Of course, it is best to keep adding letters until the intended drug name appears distinct by itself. Build order sets to guide prescribers to select the correct medication based on indication. Leverage clinical decision support so if a prescriber searches for Neo-synephrine, there will be a clinical alert that Neo-synephrine is not an approved brand name for phenylephrine injection, and to order using the generic name.

> **Myxredlin** — continued from page 4

the ADC, never scanning the barcode. An hour later, she returned to the patient's room and scanned the barcode on the infusing medication to document administration in the medication administration record (MAR). The medication was actually **MYXREDLIN** (insulin human injection) 100 units/100 mL, which looked very similar to the premixed Cardene infusion bag. Baxter manufactures both products, which have similar red and white infusion bag labels (**Figure 1**) and cartons used for light protection (**Figure 2**). The patient received approximately 40 mL of Myxredlin, was given dextrose as a precautionary measure, and fortunately, was not harmed.

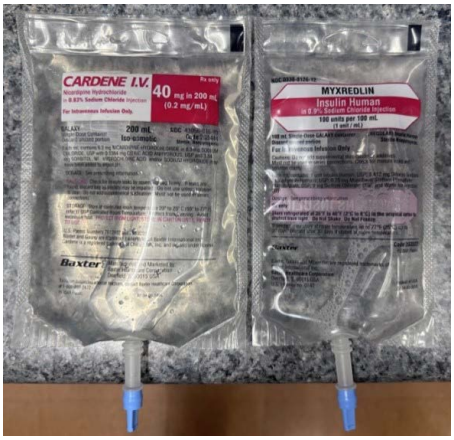

Figure 1. Similar-looking infusion bags of Cardene (left) and Myxredlin (right), made by Baxter.

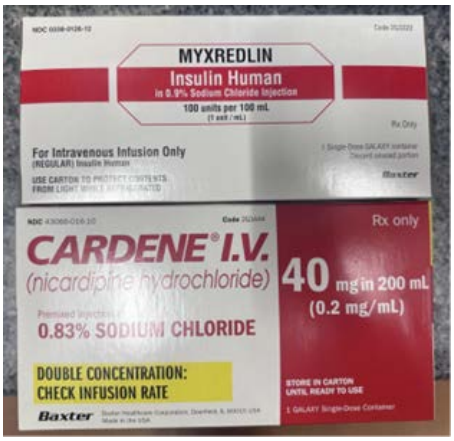

Figure 2. Cartons containing an infusion bag of Myxredlin (top) and Cardene (bottom).

Upon investigation, the hospital found that during the ADC stocking process, a pharmacy technician had scanned the barcode on only one of the Cardene cartons to access and refill the Cardene bin (following their pharmacy's process to only scan one product), and then placed a Myxredlin carton in the Cardene bin in error.

When drug products are first purchased, potential look-alike risks with other products need to be identified and addressed. When look-alike products are identified, consider purchasing the product (or one product of a problematic pair) from a different manufacturer. ISMP ***Guidelines for the Safe Use of Automated Dispensing Cabinets*** (www.ismp.org/node/1372) recommend using barcode scanning technology in the pharmacy to confirm that medications chosen for distribution to the ADC match the medications listed on the ADC fill report. Determine if your ADC has the functionality for practitioners to scan individual products (e.g., each bag or vial) when refilling the ADC, and consider requiring that process. Store look-alike products separately, and consider the use of signage or other warnings such as auxiliary labels on the infusion bags and in storage locations. We have notified the US Food and Drug Administration (FDA) about the similar-looking products and recommend the manufacturer alter one of the cartons and infusion bag labels (e.g., using color differentiation).

In our March 21, 2024 newsletter article, *Implement strategies to prevent persistent medication errors and hazards: 2024* (www.ismp.org/node/128165), we discussed how barcode medication administration (BCMA) systems are valuable tools that reduce medication administration errors, but only when used correctly. Staff must know how to properly use the system; otherwise, practitioners may employ workarounds or unsafe practices such as scanning a medication barcode *after* administration. BCMA workarounds may indicate that staff have received insufficient education related to appropriate BCMA use, or they lack knowledge about the risks involved when employing a workaround. The medication safety committee should review practices that lead to BCMA workarounds and address system issues to support safe clinical workflow. Regularly review BCMA data to identify medications commonly administered without scanning and address product issues. Observe the BCMA process to help identify potential workflow issues. Educate end-users about the importance of scanning the barcode prior to administration, not after, by using internal and external reports related to BCMA errors. Make sure this is covered during new employee orientation. Gather feedback to assess contributing factors related to workarounds.

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