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Pharmacogenomics in real life: From COVID-19 to depression, PGx testing is proving itself in practice

Advances in pharmacogenomics (PGx)—and our enhanced understanding of the individual variability of drug response—will transform our approach to the treatment of disease. PGx testing may be no silver bullet, but as a diagnostic tool used in conjunction with a process of care like CMM, it can significantly inform medication therapy management services and our approach to the treatment of disease. The current trial-and-error method will one day give way to personalized, targeted medication use.

One day. For now, the challenge is translating diagnostic discovery at the bench into management of care at the bedside.

One barrier is apprehension: Many health care professionals, vendors and payors are intimidated by the concept, explains Colleen Keenan, consultant with the Advisory Board. PGx itself may be complex, but understanding it needn't be, she says, "It's simply about analyzing the patient's genetic makeup in order to understand how they'll respond to certain medications."

For now, broad use of PGx testing is largely limited to oncology, cardiovascular and primary care, although in primary care it's typically limited to mental health diagnoses. Those are the areas with the most pharmacogenomic evidence. But more evidence is emerging, and it may hold promise in many more areas, including COVID-19.

In early 2020 Keenan and her colleagues began researching PGx to translate the science and make it more accessible to stakeholders across the industry—to help them understand what it is, what their role is and how they can use it to benefit patients, she says. They soon found an intersection between pharmacogenomics and COVID-19.

Connecting with COVID

In reviewing their early findings, three key themes from their research emerged:

1. **Drug-gene interactions:** PGx can help providers identify drug-gene interaction in patients as they relate to some of the experimental COVID-19 treatments that are happening. Drug-gene interactions are similar to drug-drug interactions. A mutation in a specific gene can cause adverse events when paired with certain drugs. By identifying those interactions, pharmacogenomics can help guide safer, more targeted COVID-19 treatments.

2. **Susceptibility to infection:** PGx testing can help clinicians understand how a patient's genetic makeup influences the likelihood of contracting the virus and the level of severity.

3. **Mental health diagnoses:** The focus here is on how pharmacogenomics can help patients with mental health diagnoses get on the right treatment faster. The connection to COVID-19? We're seeing a dramatic increase in mental health diagnoses related to the pandemic.

Guiding targeted COVID-19 treatments

Keenan offered a hypothetical example of how PGx can guide safer, more targeted COVID-19 treatments.

Mary is taking citalopram to treat her depression. However, unbeknownst to Mary or her doctor, she is a poor metabolizer of the CYP2C19 gene, which plays a role in processing at least 10% of commonly prescribed drugs. Because she's a poor metabolizer, taking citalopram puts her at risk for arrhythmias.

Mary contracts COVID-19, and her clinical team decides to treat her with hydroxychloroquine. But hydroxychloroquine puts patients at an even higher risk of arrhythmias. As a result, Mary dies from a sudden cardiac event.

"Now, this is an extreme example, but it's not out of the realm of possibility," Keenan says. Had the provider ordered pharmacogenomic testing—or already had that data stored in the EHR—they would have known the patient was a poor metabolizer of CYP2C19 and probably should not have been treated with hydroxychloroquine.

Having easy access to pharmacogenomic information, at the point-of-care, would have helped her providers make more informed treatment decisions and avoid any adverse drug events from harmful drug-gene or drug-drug-gene interactions, she says.

Genes and susceptibility

The second example relates to analyzing a patient's genetic makeup to understand their susceptibility to infection or symptom severity. Keenan addressed three genes and proteins that play important roles in the body's immune response:

- **HLA,** which are proteins that the immune system uses to identify and kill germs;
- **TMPRSS2,** which helps create a protein that coronaviruses use to enter cells in the body; and
- **ACE2,** which helps produce receptors on the surface of human cells where the coronavirus latches.

"Pharmacogenomic testing can really target these genes to see if patients have variants that would impact their body's response to the coronavirus," she explains. For example, if the patient has a mutation in her ACE2 gene, the virus could bind either more or less tightly with the cell making them more or less susceptible to COVID-19.

More evidence is needed to fully understand the genetic relationship, which would allow clinicians to make targeted prevention and treatment decisions. But if successful, the research could help identify patients at higher risk of contracting the disease, those who are going to have a more serious case or those who would benefit from a vaccine once one is developed.

In the interim, she says, understanding a person's genetic makeup in relation to COVID can allow the patient's treatment team to collaboratively counsel patients at risk to take increased preventative measures.

Genetics and mental health

Increasingly, we're seeing a strong connection between behavioral health and COVID-19. Behavioral health experts expect the surge in mental health diagnoses related to social isolation, financial difficulties and other pandemic-related factors to continue.[1]

"There's a strong amount of evidence supporting the need for PGx testing with mental health diagnoses," Keenan says. Many primary care

[1] Petterson, Steve et al. "Projected Deaths of Despair During the Coronavirus Recession," Well Being Trust. May 8, 2020. WellBeingTrust.org.

physicians actually implement pharmacogenomic testing to help get their patients on the right medications faster if they have anxiety or depression, for example. And we're also starting to see some more coverage from payors in this area.

"As primary care providers are likely to see more anxiety and depression diagnoses coming out of COVID-19, PGx testing can be a really helpful tool to help those clinicians make the most informed and targeted medication use decisions."

Moving forward

Payors are paying attention: Earlier this year, United Healthcare decided to cover a gene panel for patients with major depressive disorder or anxiety disorder diseases.[2]

Several other organizations have launched initiatives that leverage PGx to advance our understanding of COVID-19, she reports. Some are conducting research while others are centralizing that related information; some are even engaging directly with patients. (See sidebar "PGx and COVID-19" for some examples.)

"There's a lot of collaboration happening within the global genetics community," she says. Her hope is that PGx testing generates enough COVID-19-related evidence. With that evidence, providers, payors and patients may be more willing to implement PGx moving forward.

Using medication experts as part of a PGx team-based care model

Right now, only a few places have well-established PGx programs. One is the University of Florida in Gainesville. The UF Health Precision Medicine Program was established in 2011 to improve the integration of genomic data into clinical practice. Ever since, a pharmacist-led multidisciplinary team has spearheaded many clinical implementations of many different gene-drug pairs, explains Emily Cicali, Pharm.D.,

[2] "DNA Tests For Psychiatric Drugs Are Controversial But Some Insurers Are Covering Them", NPR, Oct. 17, 2019

PGx and COVID-19

Several initiatives are under way to leverage PGx to enhance the understanding of COVID-19, Keenan reports. Some are conducting research while others are centralizing that related information; some are even engaging directly with patients. She shares a few examples:

The University of Washington is working with a DC-based pharmaceutical company to do whole genome sequencing and is trying to identify links between the COVID-19 patients' genetics, their symptoms' severity and their susceptibility to contracting the illness.

A recent study, awaiting peer review, links having type A blood to a 50% increase in the likelihood that a COVID-19 patient would need to be put on a ventilator.[3]

The COVID-19 Host Genetics Initiative is centralizing data from COVID/PGx studies related to susceptibilities, severity and outcomes. They are analyzing that data and sharing results.

PharmGKB is an online information-sharing resource. It has a dedicated COVID-19 page that includes information about COVID-related drug-gene interactions.

In Finland, Negen, a genetic testing company, has created a free PGx panel focused on medications that are suggested for severe COVID-19 treatments. ■

[3] D. Ellinghaus et al., "The ABO blood group locus and a chromosome 3 gene cluster associate with SARS-CoV-2 respiratory failure in an Italian-Spanish genome-wide association analysis," *medRxiv* doi:10.1101/2020.05.31.20114991, 2020.

BCPS, clinical assistant professor, University of Florida.

Genetics in Medicine published their finding in March; Cicali was lead author.[4]

Through pragmatic clinical trials—trials that evaluate the effectiveness of interventions in real-life practice conditions—Cicali and her colleagues identified key challenges and opportunities related to implementation of PGx testing in the clinical setting.

[4] Cicali, E.J., Weitzel, K.W., Elsey, A.R. et al. Challenges and lessons learned from clinical pharmacogenomic implementation of multiple gene–drug pairs across ambulatory care settings. Genet Med 21, 2264–2274 (2019). https://doi.org/10.1038/s41436-019-0500-7

Element of success: Team-based approach

The UF College of Pharmacy leads the Precision Medicine Program. The team is led by the pharmacist, as PGx experts, as well as representatives from other areas, including pathology, informatics, the lab and, of course, the physicians. Having this team in place allows us to provide comprehensive pharmacogenomic-based management for patients.

"We have a lot of great physician champions," Cicali says. "Without them being able to express the benefits of pharmacogenomics, we wouldn't be able to influence other physicians to get on board and really be able to spread pharmacogenomic testing through our health system." Physicians value pharmacogenomic testing to help reduce the trial-and-error prescribing time. Some have experienced firsthand where medications, like tramadol, were not working for their patient and when the genetic result came back that they are a CYP2D6 poor metabolizer. It is like a light bulb turned on, and they wished they had that information up front.

Element of success: Integrating the PGx testing results into the EHR

Having access to diagnostic results at the point-of-care is essential and, when not available, is recognized as a barrier to program success. At UF, results from PGx testing are integrated in the EHR; this allows for best practice advisory alerts (BPAs) to be built-in, offering the care team access to the information. These pop-up notices can alert physicians to potential problems—that's not possible if the PGx information is added only as a PDF.

Figure 1 illustrates an alert that the physician (or other prescriber) would see in real time if the patient were a CYP2D6 poor metabolizer, and the prescriber was going to prescribe tramadol.

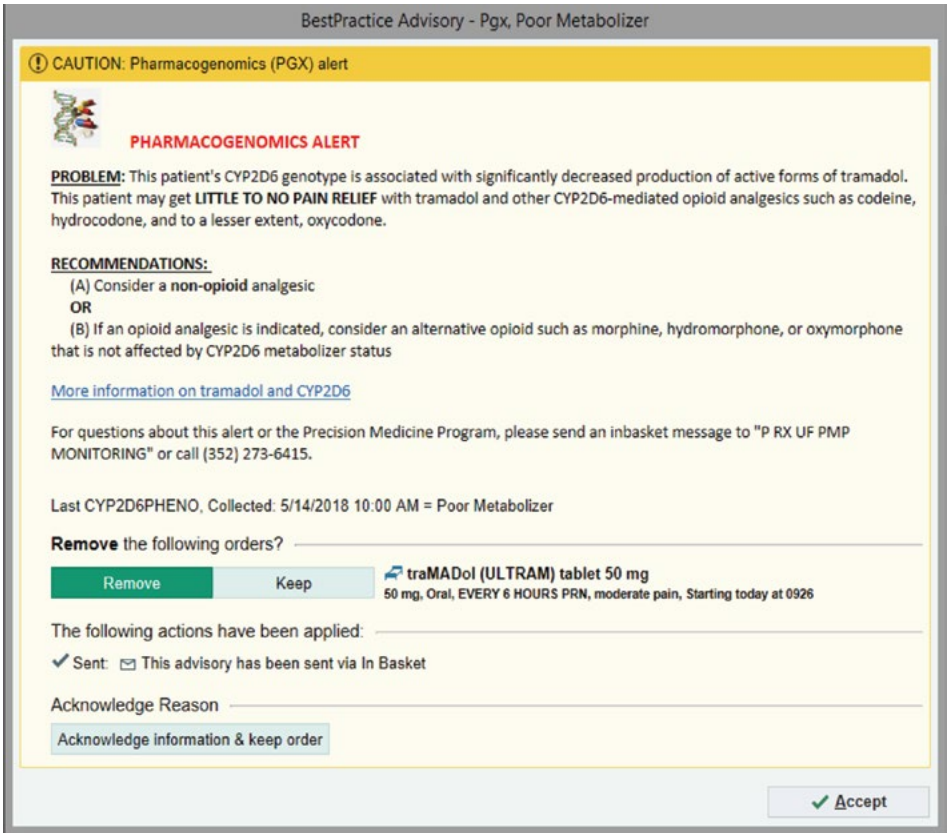


Figure 1

Testing in the real world

- **CYP2D6-opioids testing** was conducted in primary care and specialty clinics. It included adult patients with chronic pain and cancer-associated pain.

- **CYP2C19/CYP2D6-SSRIs testing** was conducted in specialty clinics. It targeted children with depression, anxiety or obsessive-compulsive disorder.

- **CYP2C19-PPIs testing** was conducted in specialty clinics and targeted children and adults who had GERD.

Researchers compared team-based, pharmacist-driven genotype-guided care versus usual care. Once the patients were randomized at baseline, the team collected a sample from all participants. Individuals randomized to the genotype-guided arm get their genotype results right away. They are populated into the EHR, and the pharmacist writes a consult note which is also placed in the EHR. (Figure 2 illustrates this process.)

At the end of the trial, all the patients can have access to results.

Learning from experience: Challenges and solutions

After the trials, the UF team invited the prescribers from all of the implementations and asked them, "Okay, well, what did we learn from this?" or, "What were some challenges that you experienced during the trial?" Then everyone reconvened to discuss, "What is the ideal solution to these challenges?"

Among the lessons learned:

- PGx results don't *unnecessarily* interrupt the workflow; best practice advisory alerts (BPAs) fire only when needed.

- PGx results need to be available at the time of the prescriber-patient encounter.

- Physician guidance and support is important, whether that comes through active clinical decision support or consult notes from the pharmacist. *It's essential to provide interpretation of the results to the physician.*

- Having a strong relationship with the laboratory is important. The lab can validate noninvasive testing methods, which is particularly important when children are involved. And if the EHR system allows it, they can ensure results are available in the medical record as discrete variables.

- Patients are enthusiastic about having that pharmacogenomics data in their medical record. All the trial patients, including those in the control arm, were genotyped. When asked, "We have your sample already collected. Do you want it run and put in your medical record?" more than 90% of the participants say yes. At the same time, patient-friendly education is important, especially in terms of managing patients' expectations before they undergo testing.

The conversations with prescribers also allowed Cicali and her team to understand the challenges they faced and collaboratively arrive at possible solutions.

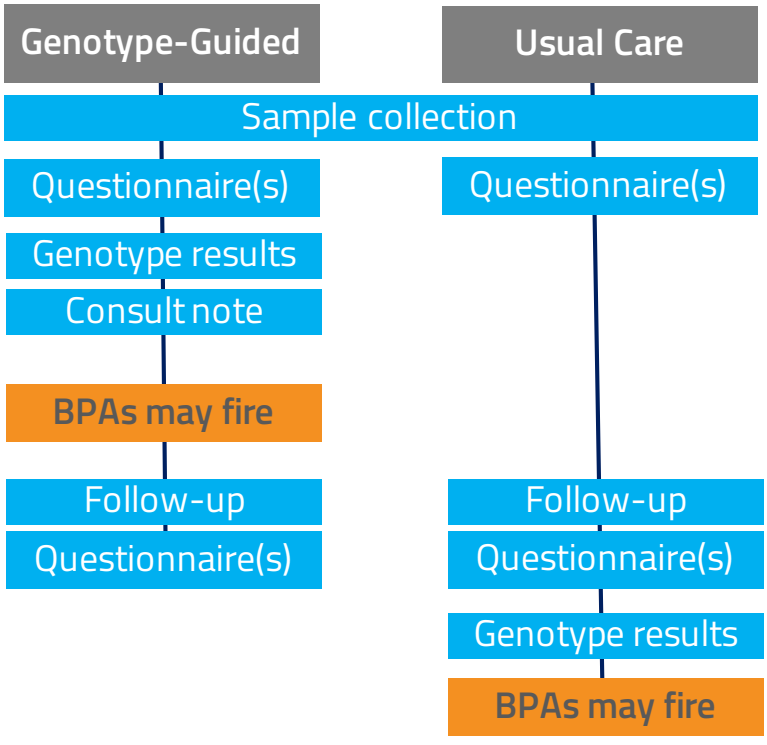


Figure 2. Genotype-guided vs Usual Care.

Challenge: Identifying who to test

IDEAL SOLUTION: Patients would be identified via electronic decision-support tools. Providers want to be able to open the chart and say, "Okay, this patient is eligible or may benefit from pharmacogenomic testing."

Although Cicali sees risk stratification as the ideal solution, it may not be the most practical, she says. There could be a first layer screening that says "this patient is on these medications that are affected by pharmacogenomics"; then it would be up to the prescriber to say, "Okay, well, how are they doing clinically? Do I need more information to actually make a decision to further guide the pharmacotherapy?"

Challenge: Provider knowledge gaps

SOLUTION: Patient-centered and case-based education is very effective for prescriber education. Giving that education upfront and throughout the study is important.

Anticipating a knowledge gap among prescribers, Cicali and her team provided pretrial education in several different ways: grand rounds presentations, web-based presentations, in-office lunch meetings, clinical in-services, continuing medical education (CME), case conferences—they even offered personal phenotyping.

Online CME had the lowest attendance. "We learned that offering CME online is just not enough incentive by itself."

The personal genotyping, in contrast, was a success. Every provider who underwent that genotyping reported it was beneficial. It got them thinking: "'Oh, I have this variant. What does that mean? What implications would this have for treating someone like me?' I think by truly engaging providers, it allows for more successful education, which is really important."

Case conferences were likewise successful. "You could almost see that light bulb turn on; providers were making the connection that pharmacogenomic results can explain some of the things they were observing in their patients. And after those case conferences, enrollment numbers would actually spike," she says. "So really, we've learned getting in front of prescribers consistently is very important."

Challenge: Availability of results in the EHR

Several physicians reported a lack of availability or recall of actual pharmacogenomic results in the EHR.

POSSIBLE SOLUTIONS:

- Instead of scanned PDFs, make sure those results are uploaded into the medical record in a discrete format, which can then fire alerts in a timely manner. That alerts the prescriber that results are available.
- Create a section of the EHR that has lifetime results and everything about pharmacogenomics: One click and everything is right there, the consult note, the results, everything in one spot.

Challenge: Interpreting the pharmacogenomic results

Prescribers highly valued our pharmacists' consult notes and the best practice alerts, said Cicali. "They didn't really want to think or remember who was tested. They just wanted to be told that information and have it tell them exactly what to do."

SOLUTION: Provide clear, concise guidance through consult notes or active alerts. "And we really try to make our alerts as concise and short as possible and really just cut to the chase. The prescribers want to know, 'What do I need to do with this information?'"

Challenge: Waiting for genotype results

SOLUTION: Genotype results should be available during patient encounters.

"When the prescriber thinks, 'I want to use pharmacogenomic information to make my decision on this particular pharmacotherapy,' they then have to order the genetic result and wait for it to be returned to actually act on it."

That means prescribers can't act on the information until the next visit, which may be months away. Cicali's team learned that acting on results at the next visit results in low adherence to recommendations. "The ideal solution here is genotype should be available during that patient encounter, so you can act on it right away."

Moving forward: Identifying and overcoming barriers

All this innovation—including access to powerful diagnostic tools—is exciting, but operationalizing PGx on a large scale remains a distant goal. Pharmacogenomic testing is not widely implemented across the health care industry today.

We still have many unanswered questions when it comes to whether this new focus on pharmacogenomics amid COVID-19 will be enough to engage all the various stakeholders, Keenan says. "So, will providers buy in to the evidence enough to dedicate time and resources to build this process into their existing workflow? Will payors have enough evidence from these studies and from the FDA to cover more pharmacogenomic tests and panels? And then on top of all that, will patients think that the process is even worth it for them?"

Keenan's answer is a very tentative "yes."

"If the various studies and innovations currently underway show that a better understanding of genetic information and susceptibility can help us return to a sense of normalcy, these players might be more willing to adopt pharmacogenomics in the long run."

What about right now? Both Keenan and Cicali want to see more organizations embrace PGx. But now may not the be ideal time. "I think it would be very hard for a hospital or a health system or a provider practice to make the case to start fresh with pharmacogenomics right now. It's expensive. You have to integrate it in the EHR to make it actually successful," Keenan says. "But I think showing the applicability, showing the evidence of what it looks like with COVID-19 and the possibility of then implementing that in the future—maybe when they're at a more stable financial status—is where we can push right now."

Now is the time for education and advocacy, they both say.

"We just need to keep educating others, keep advocating on behalf of our pharmacists on the topic to really show how the evidence is applied in different areas than just the ones we've seen so far to get different players involved," says Keenan.

Cicali agrees. "I think that we still have a challenge ahead of us to get everyone on the same page. But as long as we keep talking about its importance and urging its adoption, I think it will come." GTMR

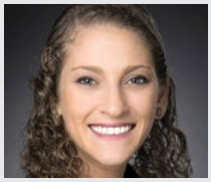
EHR vendor buy-in

Engaging EHR vendors is essential to moving PGx forward, agree Cicali and Keenan. How do we encourage EHR vendors to make the PGx module standard and not an add-on? It's a challenge: Even Cicali, who uses Epic, initially relied on a homegrown system.

"I think all we can do, as a community, is keep saying how important it is that vendors include those pharmacogenomic modules and build in standard terminology, so when patients do go from one health care system to another that information can go with them," she says.

Keenan sees it as a chicken-and-egg question. Are providers waiting for the EHR vendors to incorporate PGx results, or are vendors waiting for provider demand? Whether it's the chicken or the egg, PGx advocates need to cast a wide net. "We need to keep advocating for the importance of pharmacogenomics across the board to all the different players. Get payor buy in. Get provider buy in. Then we may see some more permanent solutions from the vendor space as well." ■

About the Experts



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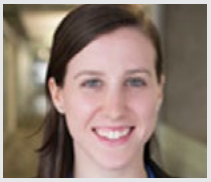
Emily Cicali, Pharm.D., received her doctor of pharmacy degree from Philadelphia College of Pharmacy, University of the Sciences in 2015. She completed a pharmacy practice residency at Tabula Rasa HealthCare in geriatric personalized medicine. After her residency, she stayed with Tabula Rasa HealthCare as a research pharmacist and was adjunct faculty at the Philadelphia College of Pharmacy. She then left to complete a fellowship in pharmacogenomics at the University of Florida. Dr. Cicali is now a clinical assistant professor in the Department of Pharmacotherapy and Translational Research. Her clinical practice is within the UF Health Precision Medicine Program, and her research interests include clinical implementation of pharmacogenomics as well as further understanding the role of phenoconversion for optimal medication safety.



Colleen Keenan
Consultant, Advisory Board

Colleen is a consultant with Advisory Board's Clinical Innovators Council, a research membership designed to help suppliers strengthen their relationships with IDNs and providers.

Colleen joined the firm in 2016 and spent over three years working on the Pharmacy Executive Forum research membership, which supports health system pharmacy leaders. She has since led research on a range of topics including opioid stewardship, drug diversion, medication reconciliation, disruptive trends impacting health system pharmacy, ambulatory clinical pharmacy models and most recently pharmacogenomics.

She graduated magna cum laude from Wake Forest University with a bachelor's degree in business enterprise management and a concentration in marketing. Colleen also minored in health policy and administration.

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