Amid COVID-19 Therapeutic Uncertainty, Experts Look for Potential Role for PGx in Managing Meds

Apr 24, 2020 | Turna Ray

NEW YORK – Since the COVID-19 pandemic started earlier this year, thousands of clinical trials have launched in an effort to better understand the SARS-CoV-2 virus and in search of drugs to successfully treat the symptoms of infection. While these studies are ongoing, doctors are scrambling to make treatment decisions for severely ill COVID-19 patients based on limited, anecdotal evidence on safety and efficacy.

This uncertainty is prompting questions in some circles about whether pharmacogenetics may be useful in helping guide treatment decisions, perhaps by identifying those who might respond particularly well to a drug, or alternatively, by flagging patients who may be at risk for life-threatening adverse events because of genetic factors or other drugs they might be taking.

Specifically, since some of the most talked about and controversial drugs being tried for COVID-19 carry the risk of arrhythmias and sudden death, experts believe there may be a role for PGx testing in identifying patients who are already genetically predisposed to such adverse events with drugs they're taking. Knowing this information in advance, they said, could help physicians make more informed treatment choices for COVID-19 patients and manage medications to avoid further increasing these risks.

For experimental COVID-19 treatment modalities where there may not be clear evidence of a drug/gene interaction, experts are hopeful that the ongoing drug studies in which researchers are exploring the role of biomarkers, such as ACE2 polymorphisms, will yield more definitive data. Ultimately, however, the real utility of PGx testing may not be in helping guide treatments for COVID-19, some predict, but as a supportive tool during the mental health pandemic that will follow.

Managing risks

Translational Software, a company that provides decision support to integrate pharmacogenetics information into patient care, recently hosted an educational webinar on the role of PGx testing during COVID-19 after several of its lab partners asked about this. During the session, Houda Hachad, CSO of Translational Software, discussed the available information in the literature, US Food and Drug Administration-approved drug labeling, and expert guidelines regarding the association between PGx variants and response to drugs being tested and prescribed for COVID-19, such as hydroxychloroquine and chloroquine.

One of the potential applications Hachad highlighted was the potential use of PGx testing to avoid drug-drug-gene interactions with hydroxychloroquine, which is currently FDA approved to treat malaria, rheumatoid arthritis, and lupus. The FDA has also granted the drug emergency use authorization, allowing its use from the Strategic National Stockpile to treat certain adults and adolescents (weighing at least 50 kg) who are hospitalized with COVID-19 and can't partake in a clinical trial.

This drug, however, is known to cause arrhythmias, such as long QT syndrome and torsades de pointes, in patients with existing cardiovascular disease, who also happen to be at increased risk for COVID-19. This week, a panel of experts convened by the National Institutes of Allergy and Infectious Diseases recommended that doctors not prescribe hydroxychloroquine together with the antibiotic azithromycin — a combination promoted in a Tweet by President Trump — because of the risk of QTc prolongation and sudden cardiac death.

In a joint statement in *Circulation*, the American Heart Association, American College of Cardiology, and Heart Rhythm Society have cautioned the same. The expert groups recommend closely monitoring the heart rhythms of patients on these drugs, and if possible, avoiding other QTc prolonging therapies.

During her presentation, Hachad noted that when patients are evaluated for the risk for QTc prolongation, physicians use a scoring system that factors in the QTc prolonging drugs they're already on. PGx testing can be helpful in this context, by identifying individuals with certain CYP2C19 and CYP2D6 genotypes that place them at increased risk for cardiac events if they are already on a long list of frequently prescribed drugs. The FDA lists several of the drugs that carry the risk of QTc prolongation in its recently published "Table of Pharmacogenetic Associations."

According to this table, individuals who are CYP2C19 poor metabolizers are at greater risk than normal metabolizers for QTc prolongation if they are receiving the antidepressant citalopram. Based on expert guidelines and FDA prescribing label information, CYP2C19 poor metabolizers should receive a lower dose of the drug.

Citalopram was the 26th most prescribed drug in the US, with more than 24 million scripts written in 2017. If a CYP2C19 poor metabolizer already on this drug were to also receive hydroxychloroquine, it could compound their risk for life-threatening arrhythmias. According to Hachad, there are numerous other examples like this where PGx information can help doctors more accurately gauge patients' cumulative risk for QT prolongation when considering whether to treat a COVID-19 patient with a drug combination like hydroxychloroquine and azithromycin.

An app to inform the public

In the process of writing a review on drugs that are currently being tried for COVID-19, pharmacogenetics expert Howard McLeod noted that there was no place for the general public to input the drugs they are on and educate themselves about the potential drug/gene, drug/drug, or drug/disease interactions they may be at risk for if they became infected with the virus and had to go on an experimental therapy.

Meanwhile, demand for hydroxychloroquine has surged despite a lack of evidence supporting its use in COVID-19 patients outside of clinical trials. "Unfortunately, we're seeing pharmacies are filling a lot of prescriptions for hydroxychloroquine," McLeod said. "Some of it is really verging on unethical behavior."

Amid the hype and politics around this drug, one of McLeod's colleagues was wondering whether to use hydroxychloroquine as prophylaxis and entered the drug into a medication management app called Pharmazam. It revealed that since he was already on an antifungal fluconazole, he would be at risk for long QT syndrome if he took hydroxychloroquine.

That example prompted McLeod to encourage Pharmazam, where he serves as senior scientific advisor, to introduce a feature where customers can learn about the potential risks associated with drugs being tried during the pandemic. In general, Phamazam's app is designed to flag potential drug/gene, drug/drug, or allergic reactions a person may have based on their medical history, lifestyle, allergies, and over-the-counter and prescription drugs they're taking.

The app can be downloaded for free, but there is a fee associated with getting PGx testing, which is performed at partner CLIA-certified and CAP-accredited labs and must be ordered by a network of physicians (though not the individual's own physician). "It's got the pharmacogenomics, but it also doesn't ignore the rest of the patient, in terms of their medicines, their drug/food interactions, drug/drug interactions, and drug/disease interactions," McLeod said.

In terms of the PGx interactions the app may flag that may be of interest in the context of the pandemic, Pharmazam CSO Taimour Langaee highlighted that polymorphisms in ABCC1 and SLCO1B1 transporters, and G6PD, are known to cause adverse effects from hydroxychloroquine. Additionally, with antiviral drugs, such as ritonavir and lopinavir, which are also being tried for COVID-19, there are transporters, as well as CYP450 and glucuronidation variants, that may impact response.

Individuals who download and enter their information into the Pharmazam app control their own data and can grant their healthcare providers permission to view it. In McLeod's own experience, when he recently took a printout of his medications from the app to his doctor's office, the medical assistant was grateful just to have a handy list of the drugs he was on.

Using pharmacogenetics to guide treatment choice, on the other hand, has had a hard slog in terms of gaining acceptance in mainstream medical circles. Many doctors have resisted incorporating information from PGx testing into their day-to-day workflows, except in very limited circumstances where there is a risk of a life-threatening adverse event. There is still differing views in medical circles regarding the utility of PGx testing to dose warfarin or clopidogrel, despite guidelines and FDA labeling supporting testing.

Physician reluctance continues to be an issue in the adoption of PGx testing, McLeod acknowledged, adding that "the healthcare system needs to be ready in order to get the full benefits of this sort of application."

Additionally, while doctors are trying to treat patients in an emergent crisis, pharmacogenetics may not be top of mind, and likely to be ignored when there is unclear messaging from health regulators about when to test patients for PGx variants that may be at issue with experimental COVID-19 drugs.

For example, the FDA-approved labels for hydroxychloroquine and chloroquine state that these drugs should be prescribed with caution in patients with G6PD deficiency, since they may be at increased risk for hemolytic anemia — where the body breaks down red blood cells faster than it can replenish them. However, the FDA labels don't explicitly recommend PGx testing.

Similarly, when the FDA put out a fact sheet for healthcare providers about the emergency use authorization of hydroxychloroquine, the agency noted that hemolytic anemia has been seen in G6PD-deficient patients, but again, doesn't provide any guidance on testing.

Advancing research

"There does seem to be some mixed messaging about G6PD" deficiency and hydroxychloroquine, noted Michelle Whirl-Carrillo, director of PharmGKB, an online knowledgebase of expertly curated information on the role of genetic variants on drug response.

PharmGKB recently launched a COVID-19 resource in an effort to collate the available information on the PGx considerations and drug-drug interactions that may come into play when treating infected patients. The webpage, which is evolving as new information comes to light, lists the drugs involved in COVID-19 trials and which of those have PGx information within PharmGKB, and notes the drugs associated with long QT syndrome. There is also a listing of genes implicated in drug adverse events and metabolism, as well as the genes involved in allowing SARS-CoV-2 viral cell entry and infection.

"The webpage is a bit of a moving target because things are changing so quickly with the research and clinical trials of the different therapies for COVID-19," said Whirl-Carrillo. "There's actually not a lot of PGx known for some of these newer, more experimental drugs," she added. "And there's not an overwhelming amount of evidence that genetic variation is going to influence greatly the outcomes for patients."

However, the bolus of drug and genomics research occurring during the pandemic is an opportunity to assess whether there is a role for genetics in personalizing COVID-19 treatment. Teri Klein, a principal investigator for PharmGKB, estimated there are more than 6,000 COVID-19 related peer-reviewed papers that have been published in the couple of months since the pandemic started.

"In the next month or so, we really will have a much better understanding of a number of these drugs," Klein said, noting that many of the experimental drug studies have rapidly enrolled and are expecting readouts on efficacy and safety relatively quickly. "In clinical trials, often you have a hard time getting a cohort," she said. "Unfortunately, given the circumstances, we don't have difficulty getting people to sign up for these experimental treatments."

Within Pharmazam's COVID19 PGx Project, experts are hoping to learn more about the pharmacogenetics of drugs being tried for COVID-19 and exploring the genetic factors that might make an individual more susceptible to infection and to experiencing severe symptoms. Particularly of interest within the project are ACE2 and TMPRSS2, genes that play role in allowing the SARS-CoV-2 virus to enter a cell and infect it. Other research teams are also studying these genes and have already identified certain ACE2 polymorphisms that appear to make patients more susceptible to SARS-CoV-2 infection.

A broader value proposition

While PGx testing may not be at the top of physicians' minds while trying to manage severely ill COVID-19 patients, Kristine Ashcraft, former CEO of YouScript, a medication management decision support tool provider, believes that the broader value proposition for PGx as a tool to keep patients out of the emergency room and hospitals is particularly relevant during this pandemic.

Genetic testing firm Invitae recently acquired PGx testing firm Genelex and its spinout YouScript, but hasn't yet articulated specific plans to apply these tools in light of the pandemic. However, Ashcraft pointed out that there are key areas of alignment between the demographic that tends to benefit most from PGx testing, and those who tend to be at risk for severe SARS-CoV-2 infection.

The elderly tend to be at the highest risk for drug-gene and drug-drug-gene adverse events because they are more likely to be on multiple therapies for chronic conditions. Meanwhile, according to the Centers for Disease Control and Prevention, those over 65 years of age, with chronic lung and kidney disease, moderate-to-severe asthma, serious heart conditions, or those who are obese, are more prone to becoming severely ill from COVID-19.

"Once somebody has COVID-19, and you're managing whatever other chronic conditions they may have in addition to trying to manage the viral infection, it becomes even more important to ensure that there aren't any drug-drug or drug-gene interactions," Ashcraft said.

And if the goal during the pandemic is to keep people out of emergency rooms and hospitals and reduce the risk of infection, then YouScript and other PGx testing firms have conducted many studies showing that patients who get tested are less likely to end up in the emergency room or hospital for a serious adverse event (see here and here).

"One of the big things we're working to do is flatten the curve, so people don't end up in the emergency room or in the hospital for a very long period of time," Ashcraft said. "Whatever we can do proactively in

the community to better manage that risk, to keep people, particularly non-COVID-19 patients, from going into the emergency room or hospital where they may get the virus, the better off we're going to be."

Managing the mental health pandemic

While researchers are working to advance drugs to treat COVID-19 and vaccines to give people immunity against the virus, the mental health impact of the pandemic will also have to be managed. This is where PGx testing may be most useful, experts in the field said.

"It is worthwhile to consider not just the utility of PGx in preventing hospitalization or changing the course of COVID-19 care," but also the impact it could have on managing "the burden on the patients that do survive a COVID-19 infection … [and] those that are suffering from the isolation of social distancing, as well as the financial hardships," said David Thacker, a clinical pharmacogenetics content specialist at Translational Software.

According to a recent *JAMA* editorial, during the SARS outbreak in 2003, there was a greater incidence of post-traumatic stress syndrome and psychological distress among patients and doctors. In communities impacted by Hurricane Ike in 2008, around 5 percent of individuals met the criteria for major depressive disorder, while one in 10 adults in New York City had symptoms of the disorder after 9/11.

"In the context of the COVID-19 pandemic, it appears likely that there will be substantial increases in anxiety and depression, substance use, loneliness, and domestic violence; and with schools closed, there is a very real possibility of an epidemic of child abuse," wrote Sandro Galea from Boston University School of Public Health, Raina Merchant from the Perelman School of Medicine, and Nicole Lurie from the Coalition for Epidemic Preparedness Innovations in Norway.

A survey in March by the American Psychiatric Association found that more than a third of polled individuals said that the pandemic was seriously impacting their mental health, nearly half said they were scared about getting the virus, and 62 percent said they feared a loved one would get it. Meanwhile, calls to substance abuse and mental health help lines increased eightfold from February to March.

As the pandemic continues, people may increasingly turn to medications to deal with the psychological wounds left by the pandemic. Drugs to treat mental health conditions, including major depressive disorder, are some of the most widely prescribed drugs in the US, but they're also highly variable and associated with unwanted side effects.

As such, one of the main areas where PGx testing has seen uptake is for personalizing psychiatry drugs. Myriad Genetics, which markets the GeneSight pharmacogenetic test, recently published a meta-analysis involving more than 1,500 patients with major depressive disorder who were enrolled in four studies, which showed that patients who received treatment based on PGx information had significantly better outcomes than those who did not.

Although PGx testing in psychiatry is not without its naysayers, doctors may reach for such testing if the use of mental health drugs increases during or after the pandemic. Genomind, a mental health-focused PGx testing company, recently took a number of steps to make it easier for physicians to deliver psychiatric care during the pandemic. Doctors can order Genomind's PGx test and send a saliva collection kit to patient's homes, which can then be mailed to the lab for analysis. Through Genomind, doctors also have access to Sharecare's HIPAA-compliant telemedicine platform for free until September, which they can use to remotely see patients and discuss PGx test results, if ordered.

"The utility of PGx during the COVID-19 crisis is more important than ever," a spokesperson for the company said. "This service is helping enable critical mental health treatment during the pandemic and Genomind is doing its best to enable as many mental health professionals as possible."

Filed Under Infectious Disease Molecular Diagnostics coronavirus pharmacogenetics pharmacogenomics Genelex Invitae Myriad