PGx Testing Reduces Adverse Drug Events, Multi-Site European Study Finds

The three-year Ubiquitous Pharmacogenomics Consortium's PREPARE study enrolled nearly 7,000 patients in seven European countries.

By Jessica Kim Cohen

PHARMACOGENETIC testing to guide treatment with drugs that are influenced by someone's genotype significantly reduces patients' risk of experiencing an adverse drug reaction, according to results from a large-scale European study.

In about 7,000 patients who all received testing with a PGx panel, researchers compared those who had an actionable genetic variant and received PGx-informed drug treatment against a control group that also had an actionable genetic variant but received standard care. They observed a 30 percent lower risk of having an adverse drug reaction in the former group, according to a paper published in *The Lancet* in February. The study, called PREemptive Pharmacogenomics Testing for Preventing Adverse Drug REactions (PREPARE), was conducted by the Ubiquitous Pharmacogenomics (U-PGx) Consortium, a group of 10 academic and government research institutions in Europe that was founded in 2016.

The findings illustrate the benefits of a PGx panel across multiple European health settings, according to Jesse Swen, a professor of pharmacogenetics in the clinical pharmacy and toxicology department at Leiden University Medical Center in The Netherlands and a principal investigator of the study. He said in an email that he hopes to see such PGx-guided prescribing integrated into standard care.

"Our study has confirmed the feasibility of genotype-guided treatment in routine clinical care in different countries, in different healthcare settings, and provides convincing evidence of the benefits of genotype-guided drug treatment with a PGx panel test," he wrote. "With the evidence from the PREPARE study, there are no more reasons to refrain from using this knowledge in the treatment of patients. Pharmacogenetics-guided drug treatment is not something for the future, it is something we can use today. We hope that clinical societies, regulators, and health insurance [providers] will acknowledge the study results, implement it in clinical practice, and provide reimbursement."

The U-PGx Consortium launched the three-year PREPARE study in 2017 to investigate whether performing preemptive PGx testing on patients as part of routine clinical care would reduce adverse drug reactions. The consortium, funded with €15 million ($15.1 million) from Horizon 2020, a European Union research and innovation funding program, sought to investigate an approach to PGx that would proactively test patients before they're prescribed a drug and develop technologies that provide recommendations on how to use such genetic information.

The study enrolled nearly 7,000 patients in seven European countries – The Netherlands, Spain, the UK, Italy, Austria, Greece, and Slovenia

– between March 2017 and June 2020. Countries were randomized to start recruiting participants either for the study arm or the control arm, and after 19 months, they switched to recruiting for the alternate arm. Participants supplied a blood or saliva sample for genotyping of about 50 genetic variants across 12 genes that affect 39 drugs included in the study. All seven of the study sites used LGC Group's SNPline platform, a PCR-based genotyping assay.

"We wanted to be sure that all the genotyping was performed in exactly the same way," Swen said during a webinar hosted by the American College of Clinical Pharmacy late last year.

To participate, patients needed to have a new drug prescribed that could be informed by PGx testing. All patients received such testing, and for patients in the study arm, PGx test results and recommendations related to their prescription were returned to their provider within seven days of starting treatment, at which point medications could be adjusted. Participants in the control group received standard care.

Patients also received a physical card – dubbed a "safety code" card – with a QR code that linked to their PGx results for prescribers and pharmacists to consult; patients in the control group received a mock plastic card. The safety code card included information on actionable drugs, genetic variants, and recommendations on dose and drug selection based on the Dutch Pharmacogenetics Working Group (DPWG). In cases where the provider's electronic health record system was capable of doing so, results were also added to a patient's EHR, where a clinical decision support system would flag prescriptions if they were contraindicated for the patient.

Based on self-reported ethnicity, 96 percent of participants had European ancestry, and the study authors acknowledged a need for future studies to include other ancestry groups.

While the analysis focused on adverse drug reactions related to the first actionable drug prescribed during the study period, researchers noted that 953 (13.7 percent) patients were later prescribed a second drug with a PGx recommendation, 79 patients (1.2 percent) were prescribed a third drug, six patients (0.1 percent) a fourth drug, and one patient a fifth drug.

Across the study, there were 3,096 serious and clinically relevant adverse drug reactions reported by 1,563 patients. The incidence of such an adverse drug reaction in patients with an actionable PGx test result was 0.21 for patients in the study arm compared to 0.28 for patients in the control arm, suggesting that the PGx intervention reduced risk of experiencing a drug-related side effect by roughly 30 percent, the authors wrote.

The effect of PGx-guided care could be even greater when considering adverse drug reactions that didn't meet the severity threshold for inclusion in the analysis, noted Minoli Perera, an associate professor of pharmacology at Northwestern Medicine who studies pharmacogenomics and was not involved in the study.

"Even the less serious adverse drug reactions are still so important," she said, because if a patient experiences side effects, they may be less likely to adhere to their medication regimen.

The PREPARE study represents another piece in a "mountain of proof" illustrating benefits of integrating PGx into standard care, Perera added. "I think it's long overdue."

In addition to a lowered risk of adverse drug reactions in patients in the study arm who had actionable PGx variants, the researchers found a similar result for all patients in the study arm compared with the control group – including those who did not have actionable PGx variants. That was unexpected, according to Swen, because patients who didn't have variants that informed their treatment should not have seen a clinical benefit.

The effect could have been caused by the addition of recruiting centers during the study that had different prescribing patterns, according to Swen. For example, adding a center that prescribes higher toxicity drugs to the control arm may have contributed to higher rates of adverse drug reactions in that group compared to the study group, regardless of whether patients in the study group had actionable variants.

In total, 93.8 percent of participants had at least one actionable genetic variant overall, and 25.2 percent had a genetic variant that informed prescribing during the study.

Physicians and pharmacists adopted 69.9 percent of the PGx-informed recommendations presented to them during the study.

Atorvastatin, a cholesterol medication, was the most common medication in the study, prescribed to 716 patients, of whom 204 had genetic variants that affected the prescription. The painkiller tramadol had the second-highest number of participants with genetic variants that affected its prescription.

The PREPARE study included recommendations for drugs used in primary care, cardiology, oncology, psychiatry, transplantation, and other specialties. Each of the seven implementation sites concentrated on recruiting patients within a particular specialty, although they weren't limited to that area. To ensure a range of drugs were included in the analysis, researchers capped each drug at 10 percent of all initial prescriptions across the study and control arms.

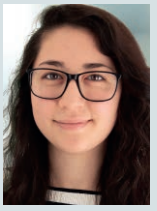
A nurse researcher conducted check-ins with participants about adverse drug reactions when they started their new medication, after four weeks, 12 weeks, and at the end of the study. Participants could also fill out an online survey at weeks two and eight.

Next, the U-PGx Consortium plans to conduct an economic analysis to assess the cost-effectiveness of preemptive PGx testing, which will be reported in a separate paper. Swen said he expects to see cost benefits. "A lot of money is spent on treating adverse drug reactions."

The U-PGx Consortium's ultimate goal is to develop processes so that personalized prescribing is available for every European citizen, Swen said. Although there's growing evidence on how genetic variation affects drug response, it isn't widely integrated into clinical care yet, he noted, with challenges including limited reimbursement and a need to present actionable results to physicians and pharmacists in a way that's easy to understand – such as through the PREPARE study's safety code card. In addition to the QR code, researchers also translated DPWG guidelines into various languages and developed educational materials for physicians, pharmacists, and patients.

Before launching the PREPARE study, the U-PGx Consortium surveyed about 400 general practitioners and 670 pharmacists in The Netherlands about their view of pharmacogenetics. Although 97.6 percent of physicians and 99.7 percent of pharmacists indicated that genetic variation might influence drug response, just 4 percent of physicians and 15 percent of pharmacists had ordered or recommended a PGx test in the prior six months. Both groups expressed concerns that PGx testing could be expensive and that the information was challenging to understand, according to Swen.

"While this concept [of pharmacogenetics] is very easy, it's very hard to get this into practice," he said. PMQ



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Jessica Kim Cohen has reported on biotechnology and health technology for seven years. At GenomeWeb, she covers precision medicine with a focus on targeted and "n-of-1" therapeutics across neurology, rare diseases, and other medical specialties. She previously was a technology beat reporter at *Modern Healthcare* and has been published in the *Chicago Reader, Chicago Health, Baltimore City Paper,* and *Baltimore*. She's based in Chicago, her hometown, and serves as president of the Asian American Journalists Association's Chicago chapter. She graduated from Johns Hopkins University in 2016.