Why do COVID-19 signs and symptoms vary so widely?

As COVID-19 spreads, its myriad manifestations in infants and youth, young and otherwise healthy adults, and elders continue to surprise and mystify the clinical and research communities and the public. The genetics of the virus coupled with the varying genetics of individuals are thought to be part of the puzzle that may provide an explanation.

Genetics plays two important roles that must, and are, being explored in this pandemic: the genetics of the virus and whether the virus is mutating and the genetics of the people infected with the virus (hosts). Genetics played a key role early in the pandemic through analysis of the viral genome, which helped scientists learn the virus’s unique properties (genetic sequence) to quickly develop testing to identify infected individuals—symptomatic, presymptomatic, or asymptomatic. Scientists continue to study the virus’s DNA to determine whether and how it may be mutating.

The answers to who is at highest risk of contracting COVID-19, how it will manifest, why some people are unable to combat the disease effectively and die, and which medications work safely and effectively in which patients may be spelled out in human (host) DNA. For example, emerging reports of COVID-19 pediatric multisystem inflammatory syndrome led one of the pediatricians interviewed to comment in a Washington Post article that her young patients with the syndrome are “a small genetic subset of children who appear to be susceptible to this crazy thing.” She and others have likened this syndrome to Kawasaki disease, which according to the National Institutes of Health Genetics Home Reference, is associated with a variation in the ITPKC gene.

Understanding the genetics at play in this pandemic is important for recognizing how the disease manifests and developing safe and effective vaccines and treatments.

Can genetic testing help identify effective therapies?

Individual genetic variation, such as inborn errors of immunity, influences how an individual’s body reacts to infections. Pathogenic variants (mutations) in a person’s DNA may increase risks for disease severity, akin to how some comorbidities (i.e., respiratory or cardiovascular disease, diabetes, immune dysfunction) are presumed risk factors for patients with COVID-19. Identifying genetic variants may help predict a person’s ability to mount a successful response to infection. Similarly, genetic makeup can heavily influence how an individual responds to treatment.

Pharmacogenetic (PGx) testing may help figure out this puzzle. PGx testing is the analysis of a person’s DNA to predict how he/she will respond to different medications—for better or worse—but such testing can help only if the genetic markers that matter when treating COVID-19 are identified. That will require more research, although some knowledge exists about how variations in DNA affect the way people metabolize drugs. Some genetic changes affect the speed at which an individual synthesizes drugs; other variants predispose individuals to potentially life-threatening side-effects from drugs. Such adverse events can include cardiac arrhythmias or sudden death.

Although few data exist now on the clinical utility of pharmacogenetic testing in patients who need treatment for COVID-19, the variation in the disease signs and symptoms suggest that genetic information could be useful to target and individualize medication therapy.
PGx established in other clinical areas; knowledge can be leveraged

PGx testing is already an established care process in some clinical areas such as cancer and rare diseases—part of a “precision medicine” approach to match the best therapy and regimen to an individual patient. FDA maintains a Table of Pharmacogenetic Associations that includes drugs with sufficient scientific evidence to identify gene-drug interactions in subsets of patients. FDA also lists therapeutic products with pharmacogenomic information in its drug labeling (Table of Pharmacogenomic Biomarkers in Drug Labeling).

Although few data exist now on the clinical utility of PGx testing in patients who need treatment for COVID-19, the variation in the disease signs and symptoms suggest that genetic information could be useful to target and individualize medication therapy.

Many medications already FDA-approved for other clinical conditions are being studied for COVID-19 treatment, some of which have known or suspected PGx effects. For example, more than 150 trials are ongoing to test hydroxychloroquine and chloroquine for COVID-19 treatment, and it is known that people with G6PD deficiency who receive chloroquine are at risk for a hemolytic crisis (destruction of red blood cells). Thus, determining whether patients have a G6PD deficiency through genetic testing would be important before enrolling patients in these trials.

In addition to aiding decisions about medications to treat the virus itself, PGx testing might be used to guide drug therapy choice for mental health disorders triggered by COVID-19 illness, social isolation, and economic stresses.

PGx testing could eventually play an important role to individualize COVID-19 treatments, reduce risk of treatment-related adverse events, and select appropriate medication doses.

Getting data and sharing outputs of COVID-19 genetic research

Efforts are underway to generate and analyze data on genetic testing’s role in prognosis and treatment. Genome-wide association studies that identify variants shared among patients who have had a severe course of illness with an unclear cause may guide researchers to potential molecular causes.

Patients may already be able to provide some of that genetic information from existing sources (i.e., prior genetic testing), or it can be generated de novo from blood or saliva samples. Whole exome sequencing and whole genome sequencing provide the highest level of information. These processes require time, effort, and prioritization. The scientific community must make conscious, concerted efforts to accurately capture and share such data.

As the recovery phase begins, research is warranted on genetics’ role in who becomes infected and symptomatic, who becomes severely ill, and which medications work best in which patients. For some patients and their treating clinicians, such genetic knowledge has potential to be lifesaving.

To learn how to become a member, contact us: clientservices@ecri.org

Policy Statement

The information contained in this Position Paper is highly perishable and reflects ECRI’s position at the time this document was prepared. This Position Paper is not intended to provide specific guidance for the care of individual patients. ECRI makes no express or implied warranties regarding the products discussed herein, including any implied warranty of merchantability or fitness for a particular use. ECRI assumes no liability or responsibility for how members use the information, comments, or opinions contained in Position Papers. All material in this Position Paper is protected by copyright, and all rights are reserved under international and Pan-American copyright conventions. Subscribers may not copy, resell, share, or reproduce information (except to print or email single report copies for authorized use within the member institution), or transfer it to third parties without prior written permission from ECRI.

About ECRI

ECRI is an independent, nonprofit organization improving the safety, quality, and cost-effectiveness of care across all healthcare settings. With a focus on patient safety, evidence-based medicine, and health technology decision solutions, ECRI is the trusted expert for healthcare leaders and agencies worldwide. The Institute for Safe Medication Practices (ISMP) is an ECRI affiliate. Visit ecri.org and follow @ECRI_Org.