How to use precision medicine to personalize COVID-19 treatment according to the patient's genes

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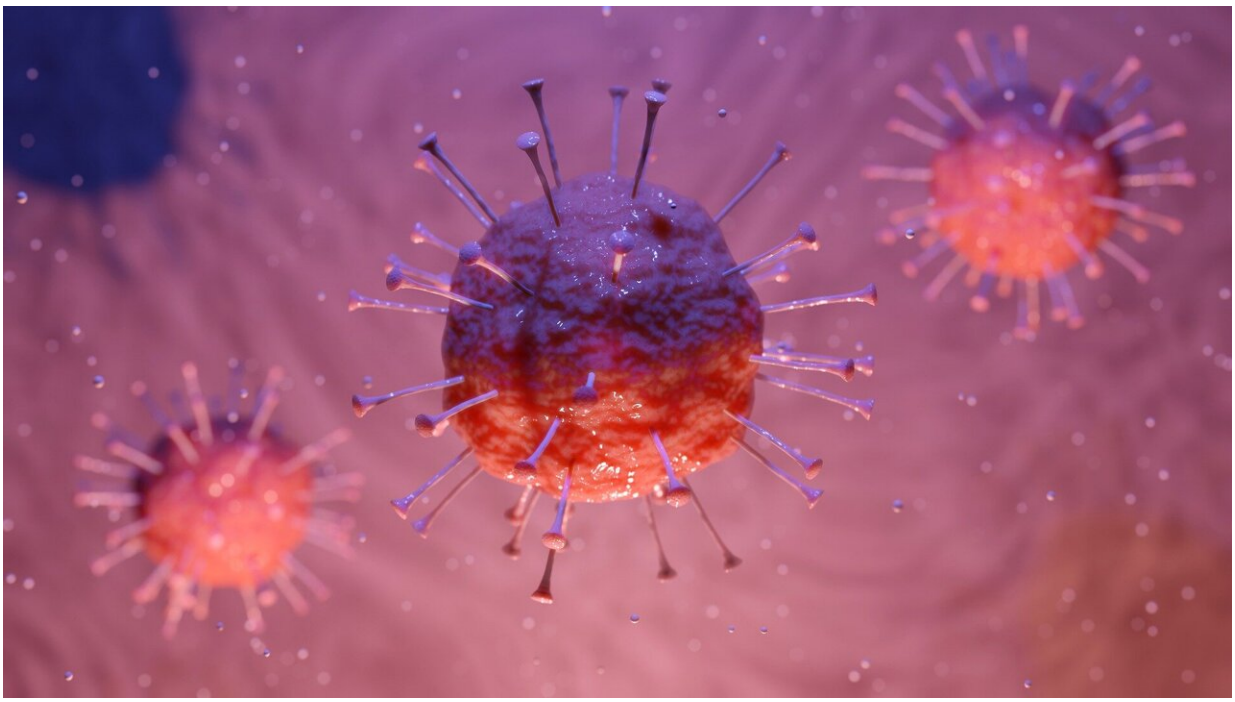

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Tom Hanks and his wife, Rita Wilson, were among the earliest celebrities to catch the novel coronavirus. In an interview at the beginning of July, Hanks described how differently COVID-19 had affected each of them in March.

"My wife lost her sense of taste and smell, she had severe nausea, she had a much higher fever than I did. I just had crippling body aches," he said. "I was very fatigued all the time and I couldn't concentrate on anything for more than about 12 minutes."

Why does COVID-19 present such different symptoms—or none at all—in different people?

Preexisting conditions can only be part of the story. Hanks is over 60 and is a type 2 diabetic, putting him in a high-risk group. Nevertheless, he survived his brush with the virus with no pneumonia and apparently without any long-lasting effects. Knowing what causes variation in different patients could help physicians tailor their treatments to individual patients—an approach known as precision medicine.

In recent years, a gene-centric approach to precision medicine has been promoted as the future of medicine. It underlies the massive effort funded by the U.S. National Institutes of Health to collect over a million DNA samples under the "All of Us" initiative that began in 2015.

But the imagined future did not include COVID-19. In the rush to find a COVID-19 vaccine and effective therapies, precision medicine has been insignificant. Why is this? And what are its potential contributions?

We are a physician geneticist and a philosopher of science who began a discussion about the promise and potential pitfalls of precision medicine before the arrival of COVID-19. If precision medicine is the future of medicine, then its application to pandemics generally, and COVID-19 in particular, may yet prove to be highly significant. But its role so far has been limited. Precision medicine must consider more than just genetics. It requires an integrative "omic" approach that must collect information from multiple sources—beyond just genes—and at scales ranging from molecules to society.

From genetics to microbes

Inherited diseases such as sickle cell anemia and Tay-Sachs disease follow a predictable pattern. But such direct genetic causes are perhaps the exception rather than the rule when it comes to health outcomes. Some heritable conditions—for instance, psoriasis or the many forms of cancer—depend on complex combinations of genes, environmental and social factors whose individual contributions to the disease are difficult to isolate. At best, the presence of certain genes constitutes a risk factor in a population but does not fully determine the outcome for an individual person carrying those genes.

The situation becomes yet more complicated for infectious diseases.

Viruses and bacteria have their own genomes that interact in complex ways with the cells in the people they infect. The genome of SARS-CoV-2 underlying COVID-19 has been extensively sequenced. Its mutations are identified and traced worldwide, helping epidemiologists understand the spread of the virus. However, the interactions between SARS-CoV-2 RNA and human DNA, and the effect on people of the virus's mutations, remain unknown.

The importance of multi-scale data

Tom Hanks and his wife caught the virus and recovered in a matter of weeks. Presumably each was infected over the course of a few minutes of exposure to another infected person, involving cellular mechanisms that operate on a timescale of milliseconds.

But the drama of their illness, and that of the many victims with far worse outcomes, is taking place in the context of a global pandemic that has already lasted months and may continue for years. People will need

to adopt changes in their behavior for weeks or months at a time.

What should a precision medicine approach be in a pandemic? The gene-centric vision of precision medicine encourages people to expect individualized gene-targeted fixes. But, genes, behavior and social groups interact over multiple timescales.

To capture all the data needed for such an approach is beyond possibility in the current crisis. A nuanced approach to the COVID-19 pandemic will depend heavily on imprecise population level public health interventions: mask-wearing, social distancing and working from home. Nevertheless, there is an opportunity to begin gathering the kinds of data that would allow for a more comprehensive precision medicine approach—one that is fully aware of the complex interactions between genomes and social behavior.

How to use precision medicine to understand COVID-19

With unlimited resources, a precision medicine approach would begin by analyzing the genomes of a large group of people already known to be exposed to SARS-CoV-2 yet asymptomatic, along with a similar-sized group with identified risk factors who are dying from the disease or are severely ill.

An early study of this kind by Precisionlife Ltd data mined genetic samples of 976 known COVID-19 cases. Of these, 68 high-risk genes were identified as risk factors for poor COVID-19 outcomes, with 17 of them deemed likely to be good targets for drug developments. But, as with all such statistical approaches, the full spectrum of causes underlying their association with the disease is not something the analysis provides. Other studies of this kind are appearing with

increasing frequency, but there is no certainty in such fast-moving areas of science. Disentangling all the relevant factors is a process that will take months to years.

To date, precision medicine has proven better suited to inherited diseases and to diseases such as cancer, involving mutations acquired during a person's lifetime, than to infectious diseases. There are examples where susceptibility to infection can be caused by malfunction of unique genes such as the family of inherited immune disorders known as agammaglobulinemia, but these are few and far between.

Many physicians assume that most diseases involve multiple genes and are thus not amenable to a precision approach. In the absence of the kind of information needed for a multi-omic approach, there is a clear challenge and opportunity for precision medicine here: If it is to be the future of medicine, in order to complement and expand our existing knowledge and approaches, it needs to shift from its gene-centric origins toward a broader view that includes variables like proteins and metabolites. It must consider the relationships between genes and their physical manifestations on scales that range from days to decades, and from molecules to the global society.

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