A nurse prepares a dose of an experimental COVID-19 vaccine July 27 in Binghamton, New York, as the National Institutes of Health and drugmaker Moderna began testing the vaccine on volunteers. "I'm excited to be part of something like this. This is huge," said one volunteer, Melissa Harting, 36, a nurse. HANS PENNINK/AP

A dose of hope

As scientists push to develop a vaccine, future of the world rests in their hands

Matt Alderton Special to USA TODAY

Companies large and small are working overtime to deliver the only thing that can truly end the COVID-19 pandemic: a vaccine.

The effort calls to mind another crash project six decades ago that similarly tested the country's scientific mettle.

On May 25, 1961, President John F. Kennedy set a goal of landing humans on the moon, and return them safely, by the end of the decade. It was inspiring, but also audacious: At that time, the longest an American had ever spent in space was 15 minutes and 22 seconds. Still, the country rallied behind Kennedy's madcap mission. And in July 1969, it met the deadline with months to spare.

In January 2020, Merriam-Webster finally updated its dictionary definition of *moon shot* to mean not just an actual space voyage but also "an extremely ambitious project or mission undertaken to achieve a monumental goal." The timing was apropos, because the United States soon launched a brand-new moon shot whose endgame is an altogether different kind of shot — a shot in the arm.

The Defense Department and the De-

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A volunteer receives an experimental COVID-19 vaccine made by Janssen Pharmaceuticals, a division of Johnson & Johnson. CHERYL GERBER/JOHNSON & JOHNSON

Vaccine

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partment of Health and Human Services launched "Operation Warp Speed" in May 2020 with a goal to develop, manufacture and deliver at scale a vaccine to inoculate the U.S. public against SARS-CoV-2, the virus that causes COVID-19.

While NASA had nearly a decade to execute its moon shot, however, Warp Speed's deadline was set at January 2021. At press time, it remained to be seen whether it would be met.

"We don't view ourselves as competing with our peers to develop and deliver a safe and effective vaccine to combat COVID-19. Together, we're competing against the virus."

Jennifer Taubert
executive vice president and worldwide chairman of Johnson & Johnson's pharmaceuticals business

"We know from experience that the best way to protect people from infectious diseases is with vaccines that enable them to mount their own immune response," says immunology expert Mary Premenko-Lanier, a research scientist at SRI International. "It's the No. 1 public health tool we have."

While Americans wait with bated breath behind millions of face masks, the government's private-sector partners search with unprecedented urgency for a silver bullet. Most of them will probably fail. That's just the nature of the research. If scientists' confidence and conviction are any indication, however, at least some will succeed.

This is a portrait of vaccine vanguards and the mission that motivates them in the face of extraordinary stress, stakes and scrutiny.

Innovations in immunity

Researchers are developing and testing nearly 200 different potential vaccines, according to the World Health Organization. From those, HHS and the

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Pentagon initially selected 14 of the most promising to get about $10 billion in federal support. The government has since winnowed its list to a handful of companies, each of which has received funding for the manufacture and distribution of at least 100 million vaccine doses.

To date, most vaccines have been one of two kinds:

- Killed vaccines, which use inactive pathogens to help the body recognize and fight off infections. Seasonal flu shots are killed vaccines.
- Live-attenuated vaccines, which use weakened versions of germs to build natural immunity. The "MMR" vaccine for measles, mumps and rubella is one of these vaccines.

However, the efforts that Operation Warp Speed has funded — by Moderna; by Pfizer in partnership with BioNTech; by AstraZeneca in partnership with the University of Oxford; by Johnson & Johnson; by Novavax; and by Sanofi in partnership with GlaxoSmithKline — are taking an entirely different approach.

Although each enterprise is using its own technique, all six of their test vaccines work basically the same way: They use weakened or benign viruses, like cold viruses, to penetrate human cells. There, the viruses have been engineered either to introduce a unique coronavirus antigen or to instruct cells to create their own, thereby activating the body's natural immune response.

"Classical vaccines are very good at inducing immune responses and very good at protection, but the testing is very rigorous, and they take a long time to make," Premenko-Lanier says. The new techniques are faster and easier. "The alternative approaches we're seeing now have been under development for a long time, but very few of them have ever been approved for an actual vaccine. ... What we're witnessing is scientific innovation converging with a novel pathogen in a way that I think is very inspiring."

Prescription: Teamwork

The alternative approaches might be quicker, but they're not necessarily better. In fact, most of them activate only one aspect of the immune system: anti-

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Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases and the nation's top infectious diseases official, gives a Senate committee an update on vaccine development in September. GRAEME JENNINGS/POOL VIA GETTY IMAGES

Vaccine update: How close is it?

'Warp Speed' contenders are now in human trials

Before they can obtain government approval, experimental vaccines must undergo a rigorous process to prove their safety and effectiveness.

According to the U.S. Food and Drug Administration, that process starts with testing vaccines under microscopes, then in animals. After that come three phases of clinical trials with human test subjects, each of which gets progressively larger in scale.

Finally, the FDA reviews evidence in favor of a vaccine before approving it, at which point it begins a final phase of study to confirm the vaccine's long-term viability while the public consumes it.

As part of Operation Warp Speed, the U.S. government has funded six promising vaccine candidates from nearly 200 contenders. Here's where each of those projects stands:

- AstraZeneca and the University of Oxford commenced a Phase 3 clinical trial in the United States in August, but paused it in September to investigate a test subject's adverse reaction. The clinical trial resumed in late October in the United States, as it had elsewhere, including in the United Kingdom, India, Brazil and South Africa.
- Johnson & Johnson launched a Phase 3 clinical trial in September, but paused it in October to examine a volunteer's adverse reaction. The trial resumed in late October.
- Moderna began a Phase 3 clinical trial in July and expects to have results by the end of 2020 or in early 2021.
- Novavax initiated a Phase 3 clinical trial in the United Kingdom in September and was expected to do the same in the United States by the end of November, according to the company.
- Pfizer and BioNTech launched a combined Phase 2/3 clinical trial in July and were expected to have results soon; at press time, results were still pending.
- Sanofi and GlaxoSmithKline started a combined Phase 1/2 clinical trial in September and expect to advance to a Phase 3 trial in December.

— Matt Alderton

Vaxart's oral vaccine is designed to block the virus at the point of infection. It's not among those getting a boost from the federal "Operation Warp Speed." VAXART

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bodies, which bind to specific pathogens and prevent them from causing the disease. Evidence so far suggests that long-term COVID-19 immunity might require a holistic response that encompasses not only antibodies, which disappear over time, but also T-cells, which are stronger, longer-lasting and can actually kill virus-infected cells in order to stop infections from spreading.

"Some patients — the elderly, for example, patients with comorbidities and people who are immunocompromised — might need an extra layer of protection," says Jeff Wolf, founder and CEO of Heat Biologics. His company is developing its own vaccine candidate that's designed to work in tandem with other vaccines by activating T-cells while they generate antibodies.

"In theory, at least, these novel vaccines might be more effective if they're put together," Premenko-Lanier says. "So instead of one vaccine, we might have multiple."

Having multiple vaccines promotes redundancy as well as efficacy. "Not every vaccine will succeed. To reach our goal, many different vaccines must be tested in clinical trials in parallel," says Sean Tucker, founder, chief scientific officer and vice president of research at Vaxart, which is developing an oral COVID-19 vaccine that would block the coronavirus at the point of infection — the mucosal lining in the nose and mouth. "Advancing multiple vaccines ensures that even if some candidates hit some unexpected obstacles ... other candidates might still be able to be tested and proven efficacious in a timely manner."

If Operation Warp Speed succeeds, that collaborative spirit will be one of the reasons why, says Jennifer Taubert, executive vice president and worldwide chairman of Johnson & Johnson's pharmaceuticals business. "We believe multiple companies working simultaneously to end this public health crisis is the right approach," Taubert says. "We don't view ourselves as competing with our peers to develop and deliver a safe and effective vaccine to combat COVID-19. Together, we're competing against the virus."

As further evidence of their collaborative approach, the CEOs of Johnson & Johnson, AstraZeneca, BioNTech, Moderna, GlaxoSmithKline, Merck, Novavax, Pfizer and Sanofi signed a pledge in September to reject scientific and regulatory shortcuts, and to seek FDA approval only if and when their vaccine candidates have been fully vetted.

"Ultimately, while we're working with a sense of urgency, developing a safe and effective vaccine remains our No. 1 priority," Taubert says.

Collaboration with academia, clinicians and government is equally essential. In order to deliver a vaccine quickly, for example, vaccine makers must expedite manufacturing and distribution. That's where the feds come in, according to medical researcher Henry Miller, who founded the FDA's Office of Biotechnol-

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ogy and is now a fellow at California's Pacific Research Institute. Companies that are funded by Operation Warp Speed, he says, are using public assistance to build the production infrastructure they'll need before they need it.

"Companies — often with the aid of government largesse — have scaled up to produce hundreds of millions of doses before they even know if they have a safe and effective vaccine," Miller says. "Ordinarily, vaccine development is very sequential. You do pre-clinical trials, which are animal studies; then you do Phase 1, 2 and 3 clinical trials; then you crunch the data and submit it to the FDA, which crunches the data again and, in the best of worlds, approves the product.

"Then, and only then, does the company invest hundreds of millions of dollars into bricks-and-mortar facilities to produce large amounts of the product. Here, that last step is occurring earlier."

Johnson & Johnson, for one, has received $1 billion from HHS to support expedited vaccine production. "Vaccine development is complex," Taubert says. "During this process, we've been able to progress some of our development activities in parallel, such as increasing our manufacturing capacity at the same time that we're conducting our large clinical trials."

Those clinical trials are yet another challenge that benefits from teamwork.

"A vaccine study is not complete until a certain number of people get naturally infected with the virus," Tucker explains. "Once that number is reached, researchers can determine whether fewer people who received the vaccine developed an infection or illness."

In other words, a vaccine can be shown as effective only if it's tested on a critical mass of volunteers, and recruiting those volunteers can be as herculean an effort as creating the vaccine in the first place. Vaccine makers must therefore partner closely with experienced clinical research sites to recruit and manage the test subjects they need.

"We have two locations that are serving as test sites for COVID-19 vaccine trials, and we have three or four times the resources committed to those trials compared to what we would have on a traditional vaccine study," says David Morin, director of comprehensive clinical research at Holston Medical Group in Kingsport, Tennessee. "Our research coordinators and investigators are working overtime to get folks safely through the clinical trial process. They're experienced, they're dedicated and they're charged-up."

A vial holds an experimental vaccine at Novavax in Gaithersburg, Maryland. ANDREW CABALLERO-REYNOLDS/AFP VIA GETTY IMAGES

People over profits

Clearly, myriad stars must align to make a COVID-19 vaccine a reality. Scientists' "charged-up" enthusiasm, however, might just be the clincher.

Like bus drivers, grocery clerks, nurses and so many others deemed essential workers, scientists have had to go to work under dangerous circumstances while others stay at home. They've had to negotiate child care and distance learning for their children. They've had to innovate new, socially-distant ways of operating inside cramped laboratories, working nights and weekends at increased speed with less space and fewer staff. And they've had to do it all with the weight of the world on their shoulders.

Still, they've done it, says Todd Zion, co-founder, president and CEO of Akston Biosciences, which hopes to commence a Phase 1 clinical trial for its own vaccine candidate before the end of the year.

"Never before have I seen a team in any capacity unite around a cause so aggressively and in a way that is so self-sacrificing," he says. "I think it speaks to the fact that we've all been affected by this pandemic; when it comes down to it, people just want to roll up their sleeves and be part of a team that's doing something."

Of course, there's money to be made, as well. But not much.

"Nobody gets rich off of vaccines," says Miller, who points out that a COVID-19 vaccine probably will be taken only once and will be priced for mass consumption — between $4 and $37 per dose, according to media reports. "That's peanuts in the pharmaceutical world."

Wolf agrees. Scientists aren't running themselves ragged to produce a vaccine in record time for pennies, he insists; they're doing it for people. "If you asked us to really search within our souls, the reason most of us are working on this is so we can bring life back to the way it was before," he says. "It's about saving lives, and making lives better."