

# Cheap Generics Might Treat COVID-19, but Obstacles Abound

Esther Landhuis

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*Editor's note: Find the latest COVID-19 news and guidance in Medscape's [Coronavirus Resource Center](#).*

First came reports about hydroxychloroquine. Then remdesivir. Then [dexamethasone](#). During this fast-moving pandemic, each time news broke about a potential treatment for COVID-19, scores of physicians felt heartened. [Yogen Kanthi, MD](#), wondered instead whether those advances would hurt patients and complicate his plans.

Kanthi had watched the novel coronavirus overwhelm hospitals in China and Italy. In late March, as COVID-19 began burning through New York City, the vascular medicine specialist and his colleagues at the University of Michigan, in Ann Arbor, braced for their own chapter of the pandemic. Local cases were climbing. Symptoms proved baffling. They were often mild but other times threatened multiple organ systems. There were no approved treatments.

But Kanthi had an idea — a possible way to prevent some of the virus's worst symptoms — and he wanted to find a way to test it. He knew blood thinners can [prevent blood clots](#) and reduce mortality from [H1N1 influenza](#). And last year, he and his colleague, rheumatologist [Jason Knight, MD, PhD](#), [published analyses](#) on a drug that suppresses inflammation and blood clots — [problems linked with severe COVID-19](#).

As the whole world has struggled to find a response, Kanthi thought his prior research might hold an answer. He thought patients infected with SARS-CoV-2, the coronavirus that causes COVID-19, might benefit from this antiplatelet agent. So when those patients started arriving at his hospital, he prepared to launch a study. What he didn't count on was how hard it would be. As he and others have discovered, even in the midst of a global pandemic, the clinical trial system in the United States is inhospitable to independent researchers.

The current system for vetting treatments has evolved in a way that caters to large pharmaceutical companies, which can employ full-time biostatisticians and clinical trial experts to run multicenter studies and pay each site tens of thousands of dollars per patient. Investigator-initiated studies — grassroots efforts with fewer resources, staff, money, and sites — are a far tougher sell to hospitals, which often don't have the resources to invest.

Independent investigators simply don't have the institutional power of pharma. And even pharmaceutical companies spend a lot of money and time to work their way through a process that is "too siloed, too bureaucratic, and in many cases too slow," said [Esther Krofah, MPP](#). Krofah is the executive director of the Milken Institute's FasterCures, a nonprofit think tank focused on accelerating medical research. She says much of what hampers medical research is "the systems we put in place, the lack of communication, the lack of coordination."

With COVID-19 still spreading rapidly in many areas throughout the United States, physician-researchers are scrambling to work around these systems in hopes of testing what they believe could be lifesaving treatments.

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## Tricky Timing and Cold Calls

To get a clinical trial going, researchers need a solid drug candidate backed by science. But even drugs already in widespread use must be approved for a new indication or patient population through the US Food and Drug Administration's (FDA's) Investigational New Drug (IND) program. That usually takes several months.

During the pandemic, institutional review boards (IRBs) have been more responsive, and the FDA — despite the increase in applications — has reduced the months-long IND process to, in some cases, less than a week. "To everyone's credit, I think things are being done quickly," said [Charles Burant, MD, PhD](#), director of the A. Alfred Taubman Medical Research Institute, which helps fund and guide efforts to move University of Michigan research findings from the lab into clinical testing.

Still, running a study that isn't exorbitantly expensive and that yields reliable results, especially in rapidly changing circumstances, is a tall order, especially when investigators must pay each site tens of thousands of dollars per patient to recruit participants, collect data, and analyze it.

The drug Kanthi had in mind, [dipyridamole](#), is typically prescribed with blood thinners to prevent strokes. It's FDA-approved. It costs about 50 cents a tablet. It has a 20-year safety record. Yet, as Kanthi was about to discover, cheap and safe generics like these — or like dexamethasone, the anti-inflammatory steroid for which promising preliminary data [were announced last month](#) — are hard to get into clinical testing, no matter how strong the [rationale](#). The cheap generics that have gained traction in

treating COVID-19, hydroxychloroquine and dexamethasone, did so on the basis of preliminary data from France and the United Kingdom (as well as, in the case of hydroxychloroquine, some [additional hyping by President Trump](#)).

In late March, Kanthi and his coworkers sketched initial plans for a single-center trial of dipyridamole in 120 patients across three arms: placebo, low-dose, and high-dose. He brought the draft proposal to Burant when their state's COVID-19 cases were rising exponentially. "We thought this was a great time to do it," Burant said.

But by the time Kanthi's study received FDA approval in mid-May, his hospital had already begun participating in different trials, making it harder to break ground. "The medical community is really jumping on this like I've never seen before," Burant said, noting that if every proposed COVID study was approved, "there would be an n of 1 for every trial."



Dr Yogen Kanthi

Over a maniacal 6-week period, Kanthi's proposal went through several iterations. He redesigned the dipyridamole study to enroll more patients across multiple sites. He cold-called friends and colleagues, pitching them the idea and asking whether anyone at their institution might consider taking part. In all, Kanthi approached more than two dozen hospitals. For each location, the progression from cold call to committee decision took a couple of weeks. "We kept hearing elements of the same message — that pharma-sponsored trials win because they're pharma." In the end, none of them signed on.

Kanthi's team revised the working protocol yet again. They scaled back the number of participants, enrolled only at the University of Michigan, and set to work.

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## The Hydroxychloroquine Roller Coaster

To further complicate matters, even as Kanthi worked on his dipyridamole study protocol, one development after another shook up the clinical-testing landscape. The FDA issued a March 28 emergency use authorization (EUA) that allowed some hospitalized COVID-19 patients to be [treated with hydroxychloroquine](#). And on May 1, another EUA [greenlighted remdesivir](#), an intravenous antiviral.

In this fast-moving pandemic, several weeks can make a huge difference. "Michigan flattened the curve just about better than anybody," Burant says. By late May, however, the [phase 2 dipyridamole trial](#) had enrolled its first patient. That occurred between two additional hydroxychloroquine developments — a large observational study that suggested the drug causes more harm than benefit, and the subsequent [retraction of this study](#) over concerns about data integrity.

The confusion and drama surrounding hydroxychloroquine have made some people more wary of hyped treatments, says Kanthi. Whereas someone with COVID-19 might have previously demanded the drugs, one of his patients recently refused to enroll in a hydroxychloroquine trial.

Then again, others suspect the volatile treatment landscape could make it harder for COVID-19 drug studies to show benefit. "Because hydroxychloroquine failed so badly, the hurdle for getting acceptance [for other drugs] may be higher," said [Josh Vogelstein, PhD](#), a statistician at Johns Hopkins University. And with some hospitals considering [dexamethasone for seriously ill patients](#), ongoing trials must now take that into account when enrolling patients. And unless a treatment has a massive effect, he said, "things like dexamethasone and remdesivir will make data analysis very tricky and increase the chance of needing additional trials down the line to prove efficacy."

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## A Frantic Search for Partners

Like Kanthi, Vogelstein and his colleagues at Johns Hopkins spent the spring working frantically to get approval for an investigator-led trial of a generic drug for COVID-19. And, like Kanthi's, their efforts were full of frustration and dead ends.

They got the idea from a 2018 mouse study that investigated the connection between certain cancer treatments and "cytokine storms," severe immune reactions marked by surges of inflammatory molecules. One particular alpha-blocker, [prazosin](#), prevented these inflammatory surges and, unlike other drugs in the study, kept the animals alive.

As [early reports](#) implicated cytokine storms in a subset of people with COVID-19–associated acute respiratory distress, the researchers began to suspect prazosin could keep patients from becoming severely ill. Among those who championed this notion were Vogelstein's dad, cancer geneticist [Bert Vogelstein, MD](#), and neurosurgeon [Chetan Bettgowda, MD, PhD](#). But to get their IRB on board with an alpha-blocker trial in COVID-19 patients, they needed human data.



Drs Josh Vogelstein and Bert Vogelstein

Chatting over dinner in mid-March, father and son hatched a plan. They figured that it might be possible to use historical claims data to investigate patients admitted to the hospital for pneumonia or acute respiratory distress. What if, the Vogelsteins wondered, those who were taking prazosin — a common blood pressure–lowering drug — had a different outcome than those who weren't?

Josh Vogelstein asked his colleagues about accessing Hopkins patient records. He called US hospitals and insurers. He talked with nationalized healthcare institutions such as those in the United Kingdom, Sweden, Denmark, Israel, and Korea. For about 2 months, Vogelstein spent 12 hours a day trying to find data and convince people to let him analyze it.

Kaiser Permanente, a comprehensive, multistate healthcare system with extensive patient electronic health records, had the closest thing to Vogelstein's Holy Grail: patient-level data from a SARS-CoV-2–infected cohort. "We know their entire drug history, medical history, and outcomes," Vogelstein said.

Several employees at Kaiser's Washington Health Research Institute, in Seattle, got to work searching patient records, paid by Vogelstein's grants and contracts.

The effort lasted about a month before Vogelstein's grants were depleted, and even then, the resulting sample was too small. Getting enough data would require similar work at more than a dozen other Kaiser facilities, each with similar soft-money constraints. "At the end of the day, we would've needed a million dollars" Vogelstein said. At that rate, the actual drug trial would cost far less than the analyses justifying it.



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Source: Kathryn Vogelstein

Drs Bert Vogelstein and Josh Vogelstein

So Vogelstein and his colleagues tried another tactic: They scoured a MarketScan historical claims database. Their retrospective analysis of more than 120,000 patients found that among those with pneumonia or acute respiratory distress who had been taking prazosin and other alpha blockers (prescribed for [benign prostatic hyperplasia](#), [hypertension](#), and other chronic conditions unrelated to ARDS), mortality was [20% to 50% lower](#) than among nonusers.

In mid-May, with a \$500K philanthropic fast grant, the team launched its [phase 2 prazosin trial](#). They're working to randomly assign 220 COVID-19 patients to receive either the study drug or standard of care for 28 days and will monitor outcomes for 60 days. Aiming to find additional collaborators, they listed their trial on the [COVID-19 Collaboration Platform](#), a website created by Hopkins biostatistician [Elizabeth Ogburn, PhD](#).

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## Collaborative Efforts

The collaboration platform aims to foster and speed interinstitutional teamwork. Ogburn created it when she and other Hopkins researchers realized that they would not enroll enough patients in their trials before the curve was flattened. And there was no way for a researcher leading a trial at one institution to link up with similar studies elsewhere, either planned or ongoing.

Physicians at other hospitals were coming to the same conclusion. "It seemed like everybody was operating in parallel in ways that were never going to get high-quality data," Ogburn said. "With coordination, we could get answers really quickly."

She hopes the platform can help like-minded investigators conduct multisite COVID-19 research using shared protocols and aggregated data. Researchers using the platform not only get collaborators but data storage, support for multisite IRB review, and the chance to consult with volunteer statisticians.

Although a collaborative approach makes sense, putting it into action isn't straightforward, Ogburn says. Biomedical research, in general, does not incentivize teamwork. Publications are the currency of academia, Ogburn says, and typically, the way you "get credit for running a trial is to maintain ownership of the data and publish on them yourself." Concerns about patient privacy and who ultimately owns the data also complicate collaboration efforts.

Another COVID-19 collaboration that has emerged is a therapeutics testing platform, [REMAP-CAP](#) (Randomized, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia). REMAP uses a big-data approach to foster collaboration. A large, randomized study built on this platform tests a variety of potential COVID-19 interventions in patients at multiple global sites.

Because REMAP follows an adaptive statistical scheme that "learns" as it goes, study investigators can add more patients to promising treatment arms while dropping the worst-performing therapies. Like a stadium built to host multiple games in perpetuity, REMAP is "a mechanism by which new ideas and new testable hypotheses can be plugged into existing infrastructure," says University of Pittsburgh trauma surgeon [Matthew Neal, MD, FACS](#), who is helping design anticoagulation trials at REMAP's Pittsburgh site.

REMAP was initially designed to test drugs for [community-acquired pneumonia](#) but [shifted to pandemic mode](#) in February. Scientists and regulators are planning new versions of the trial and are deciding which anticoagulation drugs — including dipyridamole — to test.

As they'd done in early spring, Kanthi and his colleagues are trying to prepare for future surges. When they arrive, he believes the medical teams will be better armed to test treatments more quickly and reliably. "We're prepared to respond," said Kanthi. "We'll already have all the infrastructure in place."

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