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## HOLLANDER: FIX TELEHEALTH INFRASTRUCTURE—OR AMERICA WILL BE JUST AS UNPREPARED FOR THE NEXT PANDEMIC

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## **Fix telehealth infrastructure—or America will be just as unprepared for the next pandemic**

**Judd Hollander, MD**

*Senior vice president for health care delivery innovation,*

*Associate dean for strategic health initiatives, Sidney Kimmel Medical College;*

*Vice chair for finance and health care enterprises, Department of Emergency Medicine, Thomas Jefferson University*

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Hollander spoke with  
Matthew Ong, associate editor of  
The Cancer Letter.

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## CONVERSATION WITH THE CANCER LETTER

“

No one is going to grow a program that costs them a boatload of money—and telemedicine costs a boatload of money—and then not be able to use it to care for their patients.

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As U.S. health systems switch to telehealth to connect with patients—via phone calls and online video conferencing—during the COVID-19 pandemic, providers are quickly learning that the lack of a national infrastructure for telehealth is making it difficult to reach patients.

Because of arcane licensure rules, many physicians are unable to practice medicine across state lines. Also, reimbursement for telemedicine is neither standardized nor assured, leaving hospitals to grapple with myriad public programs and individual private payers.

With rapidly vanishing basic supplies, hospitals in COVID-19 hotspots do not have the luxury of time to think about expanding access while their beds fill with dying patients.

Judd Hollander, senior vice president for health care delivery innovation and associate dean for strategic health initiatives at Sidney Kimmel Medical College at Thomas Jefferson University, says the COVID-19 crisis is making it plainly obvious how unprepared the U.S. health infrastructure is for a pandemic.

“This is a bigger problem than just state laws. It deals with federal, state and payer contracting processes,” Hollander, who is also vice chair of finance and health care enterprises in the Department of Emergency Medicine, said to *The Cancer Letter*. “It is impossible to stand up a disaster response system if you have nothing before there’s a disaster.”

*The Cancer Letter* asked one large health system, Jefferson, how it uses telehealth during the COVID-19 pandemic, how and why these capabilities were developed, and what obstacles need to be overcome.

A related story, a conversation with top executives at Sidney Kim-

mel Cancer Center at Jefferson, appears on [page 11](#).

Access to telehealth is particularly important for vulnerable populations, including patients with cancer, who require uninterrupted access to oncologists, for diagnoses, ongoing treatment, and follow-up.

Alas, the slew of systemic barriers inherent to a decentralized, private health care ecosystem means that many provider institutions are scrambling to set up telehealth programs, as states and cities shutter nonessential businesses and issue movement restriction orders and advisories.

Given the dearth of reimbursement and economic incentives, most institutions and oncology practices—even major academic centers—lack robust telehealth programs.

“No one is going to grow a program that costs them a boatload of money—and telemedicine costs a boatload of money—and then not be able to use it to care for their patients,” Hollander said.

“I think from what I know in our local cancer centers, other than ours, very few have telemedicine programs for the reasons I stated,” Hollander said. “So, now they’re left with cancer patients—who are most prone to having an adverse outcome from COVID-19—not being able to get their care.”

“It’s many, many health systems, regardless. A health system’s incentive is to take care of the patient, but by law, an insurance company’s incentive is shareholder return. So, if an insurance company has a choice to pay or not pay, and they believe the patient’s going to get the care anyway, by law they’re encouraged to not pay.”

Oncologists at Jefferson, for example, through mandates in its tele-

health program, are licensed in three states—Pennsylvania, New Jersey, and Delaware. This allows patients in the center’s catchment area to receive telehealth visits.

Nevertheless, physicians shouldn’t be required to jump through hoops to reach their patients, Hollander said.

“This is economics for the state. I have 19 state licenses. I pay for each one of them,” Hollander said. “I’ve had to get 11 sets of fingerprints to go to the FBI to verify that I’m not a criminal or a child molester to get those 19 licenses. Now, that’s insane. Can’t they talk to each other?”

“The administrative hassles become just brutal for any physician or any administrator to do. And when I’m doing that in the middle of COVID-19, physicians just don’t have time to mess with this stuff. We can’t expand licensing. It has to be easier.”

On March 17, the Centers for Medicare and Medicaid Services expanded telehealth benefits for Medicare beneficiaries—a move that will temporarily allow clinicians to get paid for providing telehealth services.

“Clinicians can bill immediately for dates of service starting March 6, 2020,” CMS said in a statement. “Telehealth services are paid under the Physician Fee Schedule at the same amount as in-person services. Medicare coinsurance and deductible still apply for these services.”

A \$2 trillion emergency relief bill passed March 27 by the House of Representatives—which, at this writing, is expected to be immediately signed by President Donald Trump—contains several provisions aimed at improving telehealth: recertification of eligibility for hospice care, reauthorization and expansion of grant programs, deductible waivers for some health plans, as well as enhanc-

ing Medicare telehealth services and increasing flexibility.

While laudable, many of these measures are temporary fixes that don’t apply to reimbursement programs and insurers that fall outside of the federal government’s jurisdiction, Hollander said.

“That means Medicare will reimburse, but I have no idea if Blue Cross and Aetna will reimburse me if I’m practicing in a state where they are the payer, but I’m not licensed,” Hollander said. “Or Medicaid as well. Again, a lack of clarity about the meaning of these federal waivers.

“The one message that hasn’t really gotten out there is the fact that these short-term fixes expire, and then they’re not going to leave us in a position to be prepared for the next crisis. We need long-term fixes that solve these problems.”

Hollander spoke with Matthew Ong, associate editor of *The Cancer Letter*.

**Matthew Ong: It seems difficult to believe, in the middle of a pandemic right now, that state laws are making it difficult for your hospital and others to practice telehealth and talk to patients across state lines. What’s happening?**

**Judd Hollander:** This is a bigger problem than just state laws. It deals with federal, state, and payer contracting processes. It is impossible to stand up a disaster response system if you have nothing before there’s a disaster.

Jefferson, actually, despite state requirements and despite poor payer reimbursement stood up a telemedicine program, making us a bit more fleet of foot during these horrible, difficult

times. And we did that at a financial loss because we believed that this was going to be medicine in the future, and we would just build the medicine of the future before the future came.

It turns out, although we weren’t smart enough to foresee COVID-19, it was fortuitous that we’re able to scale up in response to COVID-19. That being said, the major state with which we work, outside of Pennsylvania, is New Jersey.

New Jersey, I believe last Thursday night, passed into law that, for the short term patients can see their established provider. So, on Wednesday, if you were a cancer patient in New Jersey, you were not able to see your oncologist in Pennsylvania, which, frankly, made these patients have to travel to get their medical care, when it was the precise thing we were trying to avoid. Right now, that problem is obviated.

On the other hand, technically speaking, if a person is being seen at a Jefferson facility in New Jersey and is diagnosed with a new cancer, my understanding, based on the regulations that were signed into law, they could not see an oncologist in Pennsylvania. This is certainly far from ideal.

They can go to an oncologist in New Jersey, but it might be a generalist, or it might not be somebody with the specific oncologic specialty that they need. So, the law is not perfect, but it’s a heck of a lot better than it was last week.

**So, the New Jersey measure still prevents patients from seeking out new providers out of state?**

**JH:** Right. It may fix specialty care with established providers, but it doesn’t

allow referrals to oncologic specialists that cater to your type of tumor. So, it decreases the likelihood that people with new cancer diagnoses can get personalized cancer care.

**You've got a telehealth program, you've got relaxed restrictions in New Jersey, but what are some of the other limitations that Jefferson is running into? And how are patients with cancer affected?**

**JH:** The other main limitation is payer reimbursement. And in all fairness to all the payers who weren't paying for cancer care before COVID-19, they are all transiently paying for cancer care, many of them for 90 days.

There are several problems with that approach. First, this pandemic is probably going to last longer than 90 days. Second, it is likely that something like this is going to happen again. If the payers continue to say that they will stop paying in 90 days, that will also discourage other cancer providers from adopting telehealth plans.

No one is going to grow a program that costs them a boatload of money—and telemedicine costs a boatload of money—and then not be able to use it to care for their patients. People are going to go where the economic incentives are aligned. Right now, the payers are not aligning the incentives such that health systems will establish telemedicine programs.

So, what we're going to learn in the next three months is that insurance companies are going to make a mint, because they're not going to be paying for surgery and they're not going to be paying for in-person care, but they are still going to be collecting premiums. True,

they may pay something for some small amount of patients who will be getting telemedicine care, but right now it looks like a lot of premiums collected may remain in their pockets.

In 90 days, according to current policy, many payers are going to stop paying for telemedicine. And if we're lucky, we'll be past COVID-19. At that point in time we will have learned that a lot of in-person care can be handled perfectly well via telemedicine.

The unwillingness, at least at the present time, to pay for chronic care, both within and outside of cancer after this 90-day window will mean that, God forbid, COVID-20 happens, we will be no better prepared than we were from COVID-19.

**Have all private payers adopted the 90-day timeframe?**

**JH:** It's just some payers' individual policies. They all have slightly different policies, but many of the ones that we're working with expire sometime in June.

That's my concern. And now the insurance companies will say, "We don't want to subsidize your telemedicine program," but you honestly can't get innovation if it's not reimbursed. Economic incentives being what they are, people aren't going to sink a couple million dollars into a program when A, the upfront costs are expensive; and B, the downstream costs aren't going to be reimbursed.

**Is this a problem that is playing out nationwide for any health system that operates across state lines, or deals with any of these issues?**

**JH:** It's not even across state lines. It's many, many health systems, regardless. A health system's incentive is to take care of the patient, but by law, an insurance company's incentive is shareholder return. So, if an insurance company has a choice to pay or not pay, and they believe the patient's going to get the care anyway, by law they're encouraged to not pay.

**In my mind, it's a jigsaw puzzle that just doesn't come together. There are issues with licensing and problems with all the reimbursement scenarios, exacerbated by different public and private payers and state laws. Where does one start to make amends?**

**JH:** Well, you know what? I think that we've watched a lot of statements by the administration trying to do the right thing, waiving federal requirements for multiple things. But the things that they've waived federal requirements for are often not in the federal domain.

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**Insurance companies are going to make a mint, because they're not going to be paying for surgery and they're not going to be paying for in-person care, but they are still going to be collecting premiums.**



State licensing is a state issue. I'm not a lawyer, but it's my understanding that the federal government can't waive that. The individual states need to waive that. Now, it may mean that the OIG is not going to come after you for things during that period, but it might also mean that other state payers are not going to pay you when you practice unlicensed across state lines.

It may also mean that the state can come after providers who practice unlicensed, because licenses are at the state level.

No one knows what it means until the states waive it, because the federal government can waive it, but the states can still enforce it. They could enforce it a year and a half from now. It has created confusion in the middle of a crisis.

**So, we're in a multifaceted quandary and it takes super-human coordination to make telehealth work in a pandemic?**

**JH:** Yes. If a council of governors agreed to relax the rules—provided you're licensed in good standing in one state and have never had your license revoked in any other state—to just let you federalize your license and practice across state lines, that would be impactful.

But this is economics for the state. I have 19 state licenses. I pay for each one of them. I've had to get 11 sets of fingerprints to go to the FBI to verify that I'm not a criminal or a child molester to get those 19 licenses. Now, that's insane. Can't they talk to each other?

And then, actually, if I get licensed in State A on Thursday and State B is going to approve my license on Friday, I now need to get a letter from state A, who just gave me a license 24 hours ago, say-

ing I'm in good standing—before I get a license in state B, and on and on.

And so, the administrative hassles become just brutal for any physician or any administrator to do. And when I'm doing that in the middle of COVID-19, physicians just don't have time to mess with this stuff. We can't expand licensing. It has to be easier.

I would ask the question, is there a human being who's had a license to practice in 10 states, that when they apply for the 11th they get turned down for some reason? I think that's got to be a trivial fraction of a percent. This process just does not seem efficient.

**If I'm not mistaken, CMS expanded telehealth benefits for Medicare. But that only solves one part of the problem, right? Because Medicaid is managed by the states.**

**JH:** Right. So, that means Medicare will reimburse, but I have no idea if Blue Cross and Aetna will reimburse me if I'm practicing in a state where they are the payer, but I'm not licensed. Or Medicaid as well. Again, a lack of clarity about the meaning of these federal waivers.

**What about HIPAA compliance? How does that affect, say, the teleconferencing services that you're able to use?**

**JH:** I think the feds relaxing that is good. I'm very happy they did. What it really does is open up telemedicine capabilities for people that don't have HIPAA-compliant telemedicine programs.

But what it really can do is it could wreak havoc in a program like Jefferson's, because we do have HIPAA-compliant telemedicine platforms, and we want to make sure that our providers use HIPAA-compliant telemedicine platforms that meet all state regulatory requirements, and because we don't want to use something now that won't be durable for the long-term benefit of our patients.

On the other hand, if the platforms we use now fail, then we have to do what we have to do. And having those requirements relaxed is useful. So, I think relaxing those requirements will improve care for programs and people that haven't had telemedicine programs. It lets them get up on some things right away. That's a great, great step.

But it's not again going to solve a long-term problem. It's going to just be a short term solution.

**How are other providers handling this?**

**JH:** I think from what I know in our local cancer centers, other than ours, very few have telemedicine programs for the reasons I stated. So, now they're left with cancer patients—who are most prone to having an adverse outcome from COVID-19—not being able to get their care.

**Did we miss anything?**

**JH:** I don't think so. The one message that hasn't really gotten out there is the fact that these short-term fixes expire, and then they're not going to leave us in a position to be prepared for the next crisis. We need long-term fixes that solve these problems.

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Knudsen and Flomenberg spoke  
with Matthew Ong, associate  
editor of The Cancer Letter.

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CONVERSATION WITH  
THE CANCER LETTER

# Knudsen, Flomenberg: Eliminate digital health disparities; we don't want telemedicine to be for the one-percenters



**Karen E. Knudsen, MBA, PhD**

*Executive vice president of oncology services, Jefferson Health; Enterprise director, Sidney Kimmel Cancer Center; Hillary Koprowski Professor and Chair, Department of Cancer Biology, Thomas Jefferson University; Chair, Cancer Biology*

**Neal Flomenberg, MD**

*Professor and chair, Department of Medical Oncology, Director, Bone and Marrow Transplant Program, Deputy director, Sidney Kimmel Cancer Center, Thomas Jefferson University*

The Sidney Kimmel Cancer Center at Thomas Jefferson University has been developing a scalable telehealth program long before the spread of SARS-CoV-2 in the United States.

“Jefferson Health is a 14-hospital system across two states. It’s another reason why telehealth is so important for us,” said Karen Knudsen, executive vice president of oncology services at Jefferson Health and enterprise director of Sidney Kimmel Cancer Center. “We have cancer care clustered into what we call ‘SKCC advanced care hubs’ across four regions, each with subspecialists, clinical trials, and advanced care options.”

Jefferson’s telehealth program was set up at a time when there were no reimbursement incentives for telemedicine.

“Being one of the first in was critical, and allowed us to scale up in a way that I’m not sure I would call effortless, but it’s been relatively straightforward to ramp up in times of urgency, because the providers already have the core competencies needed,” Knudsen said to *The Cancer Letter*. “The patients already have the app, and all the pieces were in place.”

Since the outbreak, the cancer center has moved much of its patient visits online.

“Last week, March 16 through the 21, we completed 156 telehealth visits; March 23 to April 3, we have 234 that are scheduled,” said Neal Flomenberg, chair of the Department of Medical Oncology, director of the Blood and Marrow Transplant Program, and deputy director of the Sidney Kimmel Cancer Center at Jefferson.

“So, you can see that we’ve really, really ramped up, and that’s not been painless, but manageable,” Flomenberg said to *The Cancer Letter*. “And again, for places that didn’t get started with telehealth

before the pandemic, it’s going to be obviously a much tougher nut to crack.”

Pennsylvania Gov. Tom Wolf had issued a shutdown order for the entire state, effective March 17, closing all nonessential government offices and businesses. The protective measures, however, also meant that patients with cancer—who are at risk for developing severe complications if infected by the novel coronavirus—require nonstop connectivity if they are to reduce exposure by staying at home.

While Jefferson’s oncologists are licensed in multiple states—Pennsylvania, New Jersey, and Delaware—other providers elsewhere may not be able to reach their patients or get paid.

“The primary barrier for us, more than anything else, has either been where can you go based on your insurance, and sometimes that’s state insurance, and where is the physician licensed,” Flomenberg said. “You can’t be licensed in 50 states.

“In these unusual days I’ve just said to people, ‘Try to worry about taking care of the patients, primarily, and let’s worry about the rules and regulations secondarily.’ It’s a crisis. If people are ever going to understand, this is the time. But in a more steady-state time, those kinds of things do get a little bit more in the way and are a challenge and a barrier.”

A two-tier system that prioritizes patients who need specialty care may be one strategy for resolving the issues of access to telehealth, Flomenberg said.

“We might want to really think about perhaps a two-tiered system, in terms of the sorts of things that are dealt in a primary care setting, and the things that are dealt with in a specialty care setting, and perhaps allow a little bit more flexibility for those things that require more

complex, more unique care, more of the kinds of things that are likely to occur at a large center,” Flomenberg said.

“You think about people in rural environments. That would be empowering for them to be able to at least get some initial consultation with less of a geographic bias, less of an ordeal in terms of dragging in to a larger center.”

Cancer centers with established telehealth programs are recognizing the value and the importance of the platform, while others are rapidly expanding digital strategies, Knudsen said.

“We will have much to learn from each other once COVID is behind us, and I personally predict that we will see telehealth more deeply embedded into the cancer continuum,” Knudsen said. “In my opinion, increasing access to quality, patient-centric, specialized care that does not induce a cancer disparity should be the goal. We don’t want telemedicine to be for the one-percenters.

“In short, the urgent need to scale was readily achievable for cancer care. If we weren’t already a few years in, it would be a staggeringly challenging time to get telehealth up and running. If we hadn’t laid out that platform, I can’t imagine where we’d be right now in the middle of the COVID-19 crisis.”

Knudsen and Flomenberg spoke with Matthew Ong, associate editor of *The Cancer Letter*.

**Matthew Ong: When was Jefferson’s telehealth program set up, and how is it enabling your physicians to care for their patients at a time like this?**

**Karen Knudsen:** The telehealth initiative was actually a presidential initiative of Stephen Klasko, our president and CEO, who brought on Judd [Hollander, associate dean for strategic health initiatives at Sidney Kimmel Medical College] and team. He was committed to skating where the puck would be and introduced telehealth into our clinical care priorities. He encouraged all of the service lines and chairs to get ahead of that curve, and the Sidney Kimmel Cancer Center at Jefferson Health heard the call.

To be specific, he charged all of the providers to conduct telehealth visits well before there was reimbursement—years ago. And to his credit, Neal and the SKCC medical oncologists were some of the first to jump in.

Enthusiasm was high across the cancer service line, but Neal really set the standard for laying down expectation in the department. Our radiation oncology department headed by Adam Dicker and all our surgical oncology-intensive departments are also frequent users, and this has been to the uniform benefit of SKCC patients. We are fortunate at SKCC to have so many leaders who were ready to embrace telehealth.

**Neal Flomenberg:** I would emphasize Steve being out there, way in front, before this was a popular idea and trying to, as Karen said, anticipate where the puck was going to be. So, they set targets for us, for all the departments, in terms of trying to use it. They empowered us to be creative in different ways as to how the technology might get used.

Karen talked about us getting out in front. I think the one thing that we may have done a little bit more than others relates to the fact that there is a licensing requirement. The visit is considered to take place where the patient is as opposed to where the provider is.

We made sure that all of our docs were going to be licensed in Pennsylvania, New Jersey and Delaware, which is where the bulk of our patients come from, even though, originally, they were only going to physically see patients in Pennsylvania.

Now, we have part of the Jefferson Enterprise in New Jersey. So, there is a group that is going to physically see patients there, but we're all licensed in the three states. We've tried in the past to be creative about how we use this.

As an example of creative use, consider a patient discharged from the hospital. Before they see their outpatient physician, one of the members of the inpatient care team would reach out, typically a nurse practitioner, and have an intermediate visit before they get to their primary care team, just to make sure that everything's doing okay. That's been a fairly popular use, as an example. It's something that's a little bit different.

As you might anticipate, there were some physicians that were gung-ho in terms of new technology and some that were more tried and true, if you will, and that was also true in the patient end of things. I think that this particular experience is going to galvanize this like never before.

If my own practice is any experience—and we are trying to pull a few numbers together—the vast majority of patients that I'm interacting with now, or telehealth with, a rare patient who absolutely must come in either because they're under treatment or there's just something that can't otherwise be done. Those few come in for a physical rather than virtual visit, whereas the majority of people are being seen by telehealth.

So, just like the country may never quite be the same in terms of who's traveling into the office each day and who's work-

ing at home, I don't think health care is going to be the same, at least for places like us that have been early adopters of telehealth.

**KK:** Being one of the first in was critical, and allowed us to scale up in a way that I'm not sure I would call effortless, but it's been relatively straightforward to ramp up in times of urgency, because the providers already have the core competencies needed. The patients already have the app, and all the pieces were in place.

**NF:** In terms of just our outpatient visits, not some of these other efforts where we were trying to be creative regarding uses of telehealth that we had talked about, we were probably doing 35 to 40 a month in terms of just those standard visits. The baseline I have is January of this year. Last week, March 16 through the 21, we completed 156 telehealth visits; March 23 to April 3, we have 234 that are scheduled.

So, you can see that we've really, really ramped up, and that's not been painless, but manageable. And again, for places that didn't get started with telehealth before the pandemic, it's going to be obviously a much tougher nut to crack.

**KK:** In short, the urgent need to scale was readily achievable for cancer care. If we weren't already a few years in, it would be a staggeringly challenging time to get telehealth up and running.

It is also important to note that while many patients already had the technology, we have a very diverse catchment area, within many areas we have identified low digital literacy. As such, SKCC developed specialized strategies for this at-risk group to also access telehealth. As a Center we are committed to avoiding creation of yet another care disparity, by ensuring that telehealth is for everyone.

**How did the telehealth program help you prepare for a situation like COVID-19? But also, the flip side is, what did the program not prepare you for in a pandemic like this?**

**KK:** We were more prepared in that the providers already had the competency and the discipline for understanding how to conduct a telehealth visit, working within the confines of what can and can't be achieved, and predicting what patients would most benefit.

For example, for a patient who has completed treatment and needs a follow-up to discuss labs or imaging, there's no reason to haul that person into the clinic for 30 minutes to tell them that their test results look fine. We already adopted that mindset years ago, and this is part of our move toward cancer patient-centricity. The mission of SKCC is to improve the lives of cancer patients and their families, and appropriate use of telehealth is a major step toward that end.

Having operated in that model, the providers had confidence, the patients understood and enjoy the process, and we've had time to ensure that the quality of the telehealth visit matches that of an in-person visit. Of course, there are follow-up patients that you *do* need to lay hands on, but the providers have already completed that learning curve.

**NF:** I think that having eased into it, you continue to learn the things where you can assess the patient. And really, there are a lot of things that you can pick up. You can't listen to somebody's lungs, because you have no stethoscope, but you can get a pretty good sense as to are they having any respiratory distress, or those sorts of issues from observing them and talking to them.

And I think those of us that have done it for a while have developed a sense that there's more and more that we can actually assess in these patients if we just do more of it. If you talk to Judd, he's the guy that's got all the tricks who can show how complete an exam you can actually manage in terms of the telehealth visit. So, I think that that's really important.

I think that we're trying. It's not perfect, but we're trying to limit the number of people that come in to primarily those that are in the midst of active treatment, which brings them to the infusion center, or to the institution for a different reason. Then, we can see them in addition that day if they're due for a visit in and around this time.

Otherwise, if they don't have to come here, if there's not a compelling reason, we're trying to keep them home and keep them safe.

**KK:** A second type of visit which is highly valued in our center occurs between the patient and social worker—physician dyad teams, which can play such an important role in cancer care. Emotions are running high.

People are worried. Having psychosocial support—even if delivered by telehealth—is immensely impactful. We're actually on the precipice of launching research studies in this space to assess the overall results from both the patient and the provider perspective. This is a major priority moving forward.

**NF:** And let's be honest, there's a certain element of keeping the staff calm, too, and the providers. By dropping the number of exposures, everybody can be more comfortable. While we are primarily focused on the patients, people are people, anxieties are high, and this basically says it's better for all of us, both sides of the table.

**I'm hearing that telehealth is a capability few health systems have. And you seem to be kind of saying that as well. What is it like at other places? Is Jefferson's telehealth program unique among, say, cancer centers?**

**KK:** I'm honestly not sure if we have an overall view of what the capabilities are at other centers, and there remains much room for us to share experiences and best practices. This is something that I hope can be discussed through [the Association of American Cancer Institutes].

The AACI Slack channel was launched just last week so that the centers can have a place to rapidly share new ideas during the COVID crisis. Chatter about the use of telemedicine has only just begun.

What is already clear is that those centers with pre-existing telehealth programs are recognizing the value and the importance of the platform, and others are rapidly expanding digital strategies. We will have much to learn from each other once COVID is behind us, and I personally predict that we will see telehealth more deeply embedded into the cancer continuum.

**You were talking about patient access to telehealth and how Jefferson is being accommodating of different levels of digital literacy. How are you closing the digital divide and helping ensure that all kinds of patients are able to reach Jefferson?**

**KK:** We are very thankful to have our population science and social work teams addressing this issue together. Greg Garber, who is our head of oncology support services (and one of the world's finest people), is deeply committed to something he calls "avoidance of creating new care disparities." Especially in Philadelphia, that's just so important.

Interestingly, the disparity for telehealth begins with email, as one of the things that you need in order to do a telehealth visit is an email address. Our research teams found that across our highly varied demographic most people actually had a smartphone, but they weren't using it like a smartphone—they primarily use it for having a phone conversation or a text message, but not for email.

In order to get on a HIPAA-compliant platform for telehealth, an email address is generally needed. So, what do you do about patients who don't email, or can't download the app? This is something that Greg and team really did a great job handling, essentially by converting themselves temporarily into tech support.

The team uses whatever format needed—telephone calls, FaceTime, etc. to help guide the patient to set up an email account, download the app, and walk through a test run for patients in need of a telehealth visit. It all comes down to Gmail.

**NF:** I think Karen summarized it pretty well. The social services guys really are committed to not allowing this to become a disparity.

**KK:** And that's really key for us. Jefferson Health is a 14-hospital system across two states. It's another reason why telehealth is so important for us. We have cancer care clustered into what we call "SKCC advanced care hubs" across four regions, each with subspecialists, clinical trials, and advanced care options.

There are such different demographics in each of the regions serviced by the advanced care hubs, that the commitment that Greg and Neal have put forward to protect against creating new cancer disparities has been critical. That guiding principle permeates through every activity including telehealth. I'm really thankful for the team effort.

**That's great. Can we take a moment and talk about systemic barriers to telehealth? Why is the telehealth ecosystem sparsely developed, with many pieces that don't interlock efficiently?**

**NF:** That's where, again, we've at least tried to take the licensing issue out. That's not the complete story. I don't want this to become a dominant theme. Obviously, each state is to some extent worried about the state's well-being.

Each state typically has some outstanding institutions, and they encourage care to stay within the state, the family, etc., but sometimes that does not work out geographically or for other reasons. The primary barrier for us, more than anything else, has either been where can you go based on your insurance, and sometimes that's state insurance, and where is the physician licensed. The licensing thing is going away. It's more, where does your insurance—and that may be Medicare, Medicaid—where does that allow you to go?

**KK:** We talked about the fact that President Klasko, our CEO, made telehealth his presidential initiative years ago and said, "I know there's no reimbursement for it," at least at that time, "but I want you guys to do it." SKCC doubled down through monetary investment and time investment—in the licensing of all of the medical oncologists.

**NF:** So, we do these three states where the biggest influx of patients is going to be. But you can imagine, we might pick up some patients in Maryland. We might pick up some patients from New York. And we can't have everybody licensed everywhere. We have some specialty programs. Our uveal melanoma program is one that comes to mind that really pulls patients in from all over the country and beyond.

You can't be licensed in 50 states. In these unusual days I've just said to people, "Try to worry about taking care of the patients, primarily, and let's worry about the rules and regulations secondarily." It's a crisis. If people are ever going to understand, this is the time. But in a more steady-state time, those kinds of things do get a little bit more in the way and are a challenge and a barrier.

**KK:** I agree. How can we as a nation and we as a discipline ensure that patients have access to quality care through digital strategies like telehealth? I expect this to be an important question moving forward.

**NF:** And right now, we certainly don't want people getting on planes and flying around. We want them to stay close to the home. So, we've quietly said, "Again, put the patient first." I'm worried about that, primarily. But in the more steady-state time, this is a bigger issue.

**What are some solutions—thinking from a 30,000-foot level—for making this work? You've talked about physician licensing. You've got Medicare versus Medicaid versus private payers, different level levels of reimbursement, different state laws. When we get to, as you say, a steady-state time, where would one start?**

**KK:** Judd spoke to reimbursement issues, which loom large. In my opinion, increasing access to quality, patient-centric, specialized care that does not induce a cancer disparity should be the goal. We don't want telemedicine to be for the one percenters.

**NF:** It's an interesting question. We license physicians by state. You want to have some control. You want to have a high common denominator, maybe not the highest. You want quality, but you don't want to set an impossible bar either.

So, obviously, primary care is something that people should get close to home. But, you know, we might want to really think about perhaps a two-tiered system, in terms of the sorts of things that are dealt in a primary care setting, and the things that are dealt with in a specialty care setting, and perhaps allow a little bit more flexibility for those things that require more complex, more unique care, more of the kinds of things that are likely to occur at a large center.

You think about people in rural environments. That would be empowering for them to be able to at least get some initial consultation with less of a geographic bias, less of an ordeal in terms of dragging in to a larger center.

So, I can't say that I'd really thought about that question intensively. That's a knee jerk reaction, but that might be the kind of thing that would satisfy both.

**KK:** I think we all agree that health care should be more patient-centric and easier to navigate. Telehealth is destined to be a key part of the journey toward this end. Patients want better connectivity and more convenience.

At some level, we are the perfect test case at Jefferson, because all of us

(~33,000 employees) have ready access to telemedicine. The vast majority of us, across ranks and sites of care, have our telehealth app, JeffConnect, on our phone.

Before any of us think about showing up in the Emergency Department, we would use JeffConnect to do a quick telehealth visit. We see this as the wave forward.

We're really thankful to Jefferson and Judd's group for blazing this trail—and for allowing us to be at the ready in this surreal situation. If we hadn't laid out that platform, I can't imagine where we'd be right now in the middle of the COVID-19 crisis. The number of cancer patients who were safely seen at home instead of in the clinic is growing rapidly, thus easing the mind of both patients and their caregivers.

**NF:** We had four times as many last week, last week, as in the whole month of January and more scheduled this week.

#### Did we miss anything?

**KK:** I hope this is a call to action for the health care systems, but also for CMS and the payers to really get behind embracing telehealth for cancer patients, and to ease restrictions where possible.

**NF:** I'll always slightly editorialize. I think this is really important to do well. If you think about the fact that not all electronic medical records talk to each other particularly well, I think that we're headed toward a time when people can expect to sit down in front of their computer, or with their phone or with their tablet, and to do a lot of their health care remotely.

We need to do a better job of making sure that, 10 years from now, it's a really nice, single cohesive system, as opposed to a myriad of incompatible systems that are patched together, which is what EMRs are now.

So, hopefully, this will be a call to action that we can evolve some national standards and really do this right, so that any patient can sit down at their computer with a single app and access whoever they need.



Just like the country may never quite be the same in terms of who's traveling into the office each day and who's working at home, I don't think health care is going to be the same, at least for places like us that have been early adopters of telehealth.



— Neal Flomenberg



# Class of drugs used to treat CAR T-cell toxicity may reduce COVID-19 deaths

## Two randomized trials announced

By Paul Goldberg

A class of drugs that has been used to treat adverse events associated with CAR T-cell therapy is emerging as a potential treatment for COVID-19.

The available drugs, both interleukin-6 receptor antagonists, have the capacity to treat the cytokine release syndrome, sometimes also known as the cytokine storm syndrome, a large, rapid release of cytokines into the blood as a result of viral infections or immunotherapy.

The drugs—two of which are now being rushed into late-stage clinical trials—are approved by FDA for rheumatology indications:

- Actemra (tocilizumab), sponsored by Genentech, was approved in 2011.
- Kevzara (sarilumab), sponsored by Regeneron Pharmaceuticals and Sanofi, was approved in 2017.
- Sylvant (siltuximab), sponsored by EUSA Pharma, was ap-proved in 2014.

Tocilizumab was used in mitigation of CRS for both approved CAR T-cell therapies on the market: the Novartis agent

Kymriah (tisagenlecleucel) and the Gilead Sciences agent Yescarta (axicabtagene ciloleucel). Sarilumab isn't mentioned specifically on either of the CAR T labels, though the tisagenlecleucel label states that alternative methods of controlling CRS are acceptable after repeated failures of tocilizumab.

The sponsors of both tocilizumab and sarilumab said they are initiating clinical trials of the agents. The studies involve the Biomedical Advanced Research and Development Authority, an HHS agency focused on chemical, biological, radiological, and nuclear threats, pandemic influenza, and emerging infectious diseases.

The federal government has also obtained 10,000 vials of tocilizumab to the U.S. Strategic National Stockpile “for potential future use at the direction of the HHS,” Genentech announced.

The studies that are being launched will test whether blocking IL-6 would

stop the overactive inflammatory response in the lungs of patients who are severely or critically ill with COVID-19. The hypothesis regarding the role of IL-6 is based on preliminary data from a 20-patient single-arm study in China using tocilizumab.

An abstract from the study follows:

**Background:** In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China, which spread rapidly and has become a world-wide public health challenge. We aimed to assess the efficacy of tocilizumab in severe patients with Corona Virus Disease19 (COVID-19) and seek a new therapeutic strategy.

**Methods:** The patients diagnosed as severe or critical COVID-19 in The First Affiliated Hospital of University of Science and Technology of China (Anhui Provincial Hospital) and

Anhui Fuyang Second People's Hospital were given tocilizumab in addition to routine therapy between February 5 and February 14, 2020. The changes of clinical manifestations, CT scan image, and laboratory examinations were retrospectively analyzed.

**Findings:** Within a few days, the fever returned to normal and all other symptoms improved remarkably. Fifteen of the 20 patients (75.0%) had lowered their oxygen intake and one patient need no oxygen therapy. CT scans manifested that the lung lesion opacity absorbed in 19 patients (90.5%). The percentage of lymphocytes in peripheral blood, which decreased in 85.0% patients (17/20) before treatment (mean,  $15.52 \pm 8.89\%$ ), returned to normal in 52.6% patients (10/19) on the fifth day after treatment. Abnormally elevated C-reactive protein decreased significantly in 84.2% patients (16/19). No obvious adverse reactions were observed. Nineteen patients (90.5%) have been discharged on average 13.5 days after the treatment with tocilizumab and the rest are recovering well.

**Interpretation:** Tocilizumab is an effective treatment in severe patients of COVID-19, which provided a new therapeutic strategy for this fatal infectious disease.

The entire paper is posted [here](#).

Earlier this month, China's National Health Commission published a treatment [guideline](#) that allows the tocilizumab to be used to treat coronavirus patients who have high IL-6 levels and who show serious lung damage.

The data on tocilizumab and sarilumab fall short of a demonstration of safety and efficacy in COVID-19-related indications, and the tidbits of information

from China—as well as the news of 10,000 vials of tocilizumab going to the U.S. Strategic National Stockpile—constitute a threat to equipoise in ongoing studies, drug developers warn. It's self-evident that equipoise here is all the more important, because fundamental questions about appropriateness of these drugs for COVID-19 remain unanswered while the drugs are available for off-label use.

### SITC calls for compassionate use protocol

The Society for Immunotherapy of Cancer has published an [editorial](#), "Insights from immuno-oncology: The Society for Immunotherapy of Cancer statement on access to IL-6-targeting therapies for COVID-19" that calls for creating a compassionate use protocol based on existing templates as well as making effort for emergency approval of using of IL-6 receptor blocking antibodies by local institutional review boards within 24 hours of the request being made.

The editorial was submitted to JITC for publication and was posted on the society's website without peer review "to allow the rapid dissemination of this information."

The editorial reads:

"Although randomized data definitively showing that IL-6 receptor blockade benefits patients with COVID-19 induced pneumonitis are currently lacking, we propose that an effort should be made to maximize the availability of anti-IL-6 agents, including tocilizumab and sarilumab for use on a compassionate basis to hospitalized critically ill COVID-19 infected patients during this extraordinary situation.

"In addition, consideration should be given to focus efforts on rapidly expanding the ability of clinicians and clinical investigators to access investigational anti-IL-6 agents, in particular for those agents where Phase 1 and/or Phase 2 studies have been completed, and acceptable safety has been demonstrated. Even if the primary impact of a single dose of these drugs is to accelerate recovery and get patients off ventilator support and out of the ICU more rapidly, this could significantly decompress our severely over-burdened healthcare systems.

"We suggest that straightforward parameters including complete blood counts and differentials, serum LDH, ferritin, CRP and IL-6 be recorded in treated patients, that serum be retained for future analyses, and simple clinical parameters be assessed including time in ICU, days of hospitalization, and pulmonary parameters including FEV1, Fio2, PaO2/Fio2 ratio and oxygen need be recorded. A simple compassionate use protocol could be assembled from existing templates, and all efforts should be made for emergency approval of the use of IL-6 receptor blocking antibodies by local institutional review boards within 24 hours of the request being made.

"Additionally, consideration should be given by pharma and biotech to redirect the use of facilities and increase personnel involved in drug manufacturing and those serving as liaisons to the frontlines to facilitate drug availability. Extraordinary times call for extraordinary measures, and SITC calls on all involved, including pharmaceutical sponsors, health authorities and IRBs, to continue to move swiftly and creatively to respond and unite in removing barriers to provide our patients with care."

SITC's resources for immuno-oncology are also found on the new [SITC COVID-19 Resources](#) page, which includes:

- Online discussion forums for patient management as well as basic and translational research.
- SITC statement urging scientific journals to grant open access to COVID-19 publications.
- FDA clinical trials guidance.
- CDC COVID-19 resources.

## The tocilizumab trial

On March 23, Genentech, a member of the Roche Group, [said](#) FDA has cleared the way a randomized, double-blind, placebo-controlled phase III clinical trial, COVACTA, which would be conducted in collaboration with BARDA, Genentech said.

The trial will seek to evaluate the safety and efficacy of intravenous tocilizumab plus standard of care in hospitalized adult patients with severe COVID-19 pneumonia.

The primary and secondary endpoints include clinical status, mortality, mechanical ventilation and intensive care unit variables. Patients will be followed for 60 days post-randomization, and an interim analysis will be conducted to look for early evidence of efficacy, the company said.

Genentech has also been working with distributors to manage product supply to enable both Genentech and its distributors to meet patient needs.

“We thank the FDA for rapidly expediting the approval of this clinical trial to evaluate Actemra in critically ill patients suffering from pneumonia following coronavirus infection and we’re moving

forward to enroll as quickly as possible,” Alexander Hardy, Genentech CEO said in a statement. “Conducting this clinical trial in partnership with BARDA and providing Actemra to support the national stockpile, through the efforts of Secretary Azar and HHS, are important examples of how the U.S. government the biotechnology industry and health-care communities are working together in response to this public health crisis.”

The company said that several independent clinical trials have begun globally to explore the efficacy and safety of Actemra for the treatment of patients with COVID-19 pneumonia. “However, this new trial is vital, because there are no well-controlled studies and limited published evidence on the safety or efficacy of Actemra in the treatment of patients suffering from COVID-19,” the company said.

## The sarilumab trial

On March 16, Regeneron and Sanofi [said](#) they have started a clinical program evaluating sarilumab.

This phase II/III, randomized, multi-center, double-blind, phase II/III trial has an adaptive design with two parts and is anticipated to enroll up to 400 patients, the companies said. The trial will begin in New York and will recruit patients at approximately 16 U.S. sites.

The trial uses an adaptive design. To be eligible, patients must be hospitalized with laboratory-confirmed COVID-19 that is classified as severe or critical, or who are suffering from multi-organ dysfunction. All patients must have pneumonia and fever. After receiving the study dose, patients will be assessed for 60 days, or until hospital discharge or death.

In the phase II component of the trial, patients will be randomized 2:2:1 into three groups: sarilumab high dose, sar-

ilumab low dose, and placebo. The primary endpoint is reduction of fever and the secondary endpoint is decreased need for supplemental oxygen.

The phase II findings will be utilized in an adaptive manner to determine transition into phase III, helping to determine the endpoints, patient numbers and doses. The second, larger part of the trial will evaluate the improvement in longer-term outcomes including preventing death and reducing the need for mechanical ventilation, supplemental oxygen and/or hospitalization.

If the trial continues with all three treatment arms to the end, it is expected to enroll approximately 400 patients, depending on the status of the COVID-19 outbreak and the proportion of patients with severe COVID-19 and high levels of IL-6.

“To initiate this trial quickly, so that the results may inform evidence-based treatment of this ongoing pandemic, Regeneron and Sanofi have worked closely with FDA and the Biomedical Advanced Research and Development Authority,” George D. Yancopoulos, co-founder, president and chief scientific officer of Regeneron, said in a statement. “Data from China suggest that the IL-6 pathway may play an important role in the overactive inflammatory response in the lungs of patients with COVID-19. Despite this encouraging finding, it’s imperative to conduct a properly designed, randomized trial to understand the true impact.

“Our trial is the first controlled trial in the U.S. to evaluate the effect of IL-6 inhibition prospectively in COVID-19 patients. In addition to our Kevzara program, Regeneron is also rapidly advancing a novel antibody cocktail for the prevention and treatment of COVID-19, which we hope to have available for human testing this summer. Both of these programs are made possible by our unprecedented end-to-end antibody

“

There is some increasing evidence (although still controversial) that COVID-19 is associated with a component of CRS, and that CRS may accompany terminal event of respiratory failure and death.

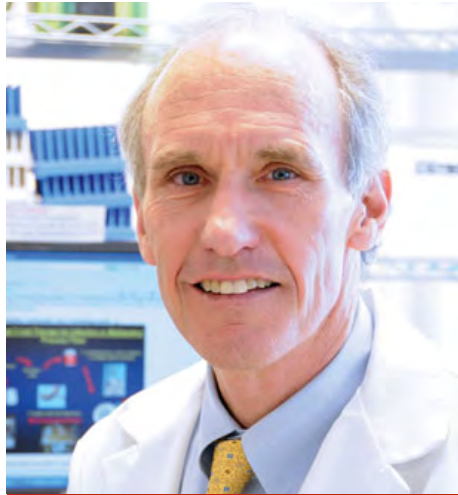
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— John DiPersio and Armin Ghobadi

discovery, development and manufacturing technologies, starting with our proprietary VelocImmune human antibody mouse, and incorporating our associated rapid manufacturing technologies designed to select and produce the best neutralizing antibodies. Collectively, these technologies expedite a typically years-long process into a matter of months. This same technology was applied to the Ebola virus, where our therapy, REGN-EB3, was shown to dramatically improve survival in infected patients last year.”

## Evaluating the IL-6 hypothesis

To delve deeper into the fundamental questions that surround the role treatments for the cytokine release syndrome—especially IL-6 receptor antagonists—may play in COVID-19 indications, The Cancer Letter administered a questionnaire to the following experts:



**Carl H. June, MD**

*Richard W. Vague Professor in Immunotherapy, Department of Pathology and Laboratory Medicine, Perelman School of Medicine of the University of Pennsylvania*



**Armin Ghobadi, MD**

*Associate professor of Medicine, Washington University School of Medicine in St. Louis*



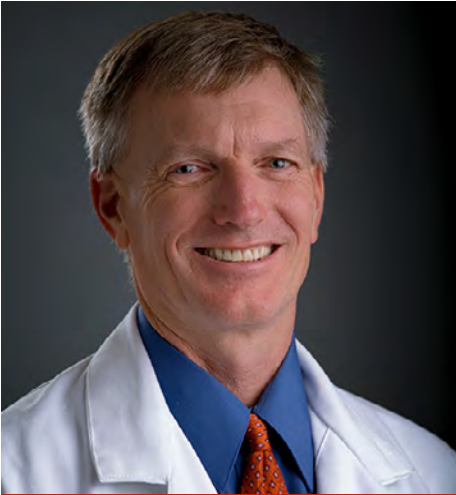
**John DiPersio, MD, PhD**

*Chief, Division of Oncology, and Virginia E. and Samuel J. Golman Endowed, Professor of Oncology, Washington, University School of Medicine in St. Louis; Deputy director, Siteman Cancer Center*



**Paolo A. Ascierto, MD**

*Director, Unit of Melanoma, Cancer Immunotherapy and Innovative Therapy, National Tumor Institute Fondazione G. Pascale in Naples, Italy*



### Randy Q. Cron, MD, PhD

Professor of pediatrics and medicine,  
Director of the Division of Pediatric  
Rheumatology at the University of  
Alabama at Birmingham;  
Author of "*Cytokine Storm Syndrome*,"  
a textbook on cytokine storms

## 1. What is cytokine release or cytokine storm syndrome

**Carl H. June:** First of all, as far as the terminology goes, I prefer to distinguish cytokine release syndrome from cytokine storm.

Cytokine release syndrome is due to a targeted immune response and can be delayed in onset. With CAR T-cell therapy we have seen cytokine release syndrome delayed for as long as 50 days after the infusion of CAR T in patients with leukemia; this is an on-target response that almost always correlates with beneficial anticancer effects.

In contrast, cytokine storm is a nonspecific release of cytokines and chemokines by many cells in the immune system and can occur immediately. The scientific community became commonly aware of cytokine storms about a decade ago, after the administration of super agonistic administration CD28 antibodies to healthy volunteers.

However, during the Cold War, both the United States government and the Soviet Union studied the use of bacterial superantigens, such as staphylococcus enterotoxin B as biologic warfare agents. These bacterial superantigens can kill mice and larger animals within hours after administration.

**John DiPersio and Armin Ghobadi:** CRS is an inflammatory syndrome, which is due to the excessive activation of human monocytes/macrophages by multiple etiologic agents, which either directly activate monocytes or activate macrophages via the activation of T cells.

In the case of CRS associated with CAR T therapy, it is the interaction of activated and rapidly expanding CAR T with their target cells and the release and/or direct interaction with neighboring monocytes to release specific inflammatory cytokines, such as IL-6 and IL-1, as well as other cytokines and chemokines that result in CRS (fever, edema, capillary leak, new oxygen requirement).

The release of IL-6 by monocytes is largely responsible for the fevers associated with CRS; however, the neurotoxicity may or may not be related to IL-6 and may be mediated by other cytokines and chemokines, such as IL-1, TNF, GM-CSF, and even other vascular trophic cytokines such as VEGF, Angiopoietin-1 etc.

The entire syndrome mimics other macrophage activation syndromes, such as HLH (primary or secondary), and is manifested by elevation of temperature, vascular leak, hypoxia and then even altered mental status.

All can be mild, moderate or life-threatening/ending. Serum markers can be used to follow the disease, such as IL-6 levels, ferritin and C-reactive protein (CRP).

There is some increasing evidence (although still controversial) that COVID-19 is associated with a component of CRS, and that CRS may accompany terminal event of respiratory failure and death, which is not necessarily due to progression of pneumonia, but to excessive macrophage activation syndrome (MAS), which is driving terminal events such as hypotension, vascular leak and increasing O<sub>2</sub> requirements from the both the inflammation induced by the pneumonia, but also to the body's immune response (excessive immune response resulting in CRS and MAS) to the viral infection and to the pneumonia caused by COVID-19.



### Winn Chatham, MD

Professor of medicine, clinical  
immunology, and rheumatology,  
Senior scientist at the Comprehensive  
Arthritis, Musculoskeletal, Bone and  
Autoimmunity Center;  
Director of Rheumatology Clinical Services,  
University of Alabama at Birmingham

**Paolo A. Ascierto:** Cytokine release or cytokine storm is a severe systemic inflammatory response to an injury.

**Randy Q. Cron and W. Winn Chatham:** An illness complication whereby there is unchecked immune activation leading to ongoing accentuated release of pro-inflammatory cytokines that cause injury to multiple organs, frequently resulting in death if not treated.

2. Is it accurate to say that some of the people who are dying from COVID-19 are experiencing a cytokine storm syndrome?

**June:** I have no first-hand knowledge of the immunopathology in COVID-19. However, a [preprint](#) from China has some intriguing data in about 20 COVID-19 patients who had progressed on supportive care for about five days and were then given an infusion of tocilizumab. The temporal relationship of the fall in C-reactive protein and the resolution of fever are compelling in the data that is shown.

**DiPersio and Ghobadi:** See above. Still controversial, but yes, we believe that there is increasing evidence that CRS is occurring co-incident with the progressive pneumonia and in severe cases may be driving the pathology and increasing the risk of death above and beyond what would be expected by the viral infection by itself.

**Ascierto:** Xu et al. (chinaXiv:202003.00026) reported data from biopsy samples coming from autopsy in a patient who died for COVID-19, suggested that an inflammatory factor or a cytokine storm have occurred. They also found that aberrant pathogenic T cells and inflammatory

monocytes are rapidly activated and are responsible of an inflammatory storm.

**Cron and Chatham:** There are increasing reports of series of patients critically ill with COVID-19 that have clinical features and blood abnormalities that are hallmarks of CSS (sepsis syndrome, ARDS, coagulopathy, hepatobiliary dysfunction, cytopenias). There are no formal studies we have seen yet that would answer the question of what percentage of deaths from COVID-19 are attributable to CSS as this is not routinely being assessed (it needs to be!).

3. If yes, how is it different from the cytokine storms observed in some people receiving CAR T-cell therapy? In CAR T, the cytokine storm is an IL-6 storm. Is this the same with COVID-19?

**June:** Cytokine release syndrome is best thought of as a subset of secondary haemophagocytic lymphohistiocytosis (HLH), which also goes by an alternative name of macrophage activation syndrome.

Related to secondary HLH are cases of primary HLH generally seen by pediatricians that are caused by certain genetic lesions. It is possible that some of the COVID-19 patients that have hyper-inflammation have some of the predisposing genetic abnormalities that are found in other people with secondary HLH.

It is good to remember that a subset of patients with systemic viral infections are diagnosed with secondary HLH. In many of these patients, interleukin-6 is at the center of the immunopathology, along with high levels of interferon-gamma and serum ferritin levels.

**DiPersio and Ghobadi:** See above, again. We have not seen the inflammatory state of COVID-19 as well characterized as it has been with CAR T-associated CRS.

This needs to be done. This includes cytokine assays, fibrinogen, ferritin, CRP, IL-6, etc., as well as neurocognitive testing. It would appear different than CAR T in one important feature, and that is CRS and fever is an acute and dramatic early feature of CAR T CRS, while the CRS associated with feature of CAR T in an acute and early and fulminant (in first 1-4 days), while the CRS associated with COVID-19 is slow to develop and appears late with fevers and progressive pulmonary insufficiency.

Also, the fatal events in CAR T CRS (neurotoxicity) occurs late with progressive neurotoxicity—still, we have no idea what is causing this, although IL-1 has been implicated in some preclinical studies which may not have any relevance to what we see in patients receiving CAR T—when the “CRS” and CRS markers have often returned to normal, while the COVID-19 CRS are more associated with the terminal events high fever and worsening pneumonia and excessive tissue damage and death.

**Ascierto:** In CAR T-cell therapy the cytokine release syndrome is due to the activation of T cells armed with CAR, while in the COVID-19 such aberrant response seems to be mainly due to monocytes/macrophages.

According to Xu et al., and previous studies in SARS and MERS, it seems that IL-6 is still the most important cytokine involved in the cytokine storm by COVID-19.

**Cron and Chatham:** The clinical phenotype is the same and IL-6 levels have been noted to be elevated in COVID-19 critical illness, but the principal inflam-

matory mediators in COVID-19 CSS have not been well characterized as of yet.

**4. Are the parallels with other viral syndromes, such as coxsackievirus, significant here?**

**June:** Exactly, it is likely that COVID-19 cases of hyper-inflammation are the same syndrome as seen in other systemic viral infection, such as with some strains of influenza (1918 pandemic) and beta coxsackie viruses such as MERS and SARS.

**DiPersio and Ghobadi:** No, not really.

**Ascierto:** Even if some other viral infection could hypothetically trigger a cytokine storm, coronavirus infections seems to be those with a higher incidence of such condition.

**Cron and Chatham:** Other viruses (particularly influenza and herpes viruses such as EBV, CMV, HSV) are well known triggers of CSS in genetically susceptible individuals.

**5. Is it true that the cytokine storm can be diagnosed with the serum ferritin blood test? Are there any other tests that seem relevant?**

**June:** Extreme elevations of serum ferritin requiring dilutions by the laboratory technicians as well as high levels of C-Reactive Protein are characteristic if not pathognomonic of cytokine release syndrome and secondary HLH.

Our group, in conjunction with the scientists at Children's Hospital in Philadelphia, have studied the cytokines

and other biomarkers in serum that are found elevated in cytokine release syndrome after CAR T and have compared this to markers that are found elevated in sepsis (PMID: 27632680 and 27076371).

**DiPersio and Ghobadi:** See above. Fibrinogen, ferritin, CRP, cytokine levels (especially IL-6).

**Ascierto:** From my point of view the evaluation of serum IL-6, C-reactive protein (which is strongly related to IL-6 level) and ferritin are the most relevant

**Cron and Chatham:** An elevated serum ferritin should be a danger signal that should prompt immediate assessment for CSS. The higher the ferritin level, the greater the likelihood of CSS.

**6. Would tocilizumab be an appropriate drug to try for the treatment of COVID-19?**

**June:** It is really interesting that the first use of tocilizumab for hyper-inflammation and secondary HLH was in the case of Emily Whitehead, our first pediatric patient given the experimental form of Kymriah (PMID 23527958).

It clearly saved her life, and later became co-labeled by the FDA for therapy of CRS after CAR T for both Kymriah and axicab [Yescarta]. I think it is highly likely that interruption of interleukin-6 signaling (and probably IL-1) will be beneficial in the subset of patients with COVID-19 that have hyper-inflammation and immunopathology.

There are many questions in this area, such as when to initiate such therapy, how long should it be given, and should it be given preemptively rather only in reaction to progressive ventilatory failure.

Fortunately, many trials are being started in China and here in the United States that will provide answers to these questions.

One major issue that needs to be answered is whether or not this therapy will lead to delayed clearance of the virus and therefore potentially more patients who could be asymptomatic vectors of the virus?

**DiPersio and Ghobadi:** Yes. Both tocic FDA approved IL-6R and sarilumab (IL-6R blocking agent from Regeneron/Sanofi and approved in Canada but not in the U.S.). Remember, it is not a treatment for COVID-19 but a treatment of the life-threatening and terminal CRS events associated with COVID-19 (high fever, progressive O<sub>2</sub> demands or post-intubation).

I know that Regeneron has sent out some feelers to intensivists around the country for a clinical trial that they are considering. Also, other agents could be considered including the IL-6 antibody (siltuximab) and the IL-1 receptor antagonist, anikinra (Kineret).

All should be considered especially in the context of clinical trials if possible. Finally, we are proposing a similar intervention with JAK1/2 inhibitors in these terminally ill patients that are intubated and febrile to reduce death associated with CRS from COVID-19. We are considering several JAK inhibitors produced by several companies (Incyte and Lilly) in the context of a clinical trial here at Washington University and at other centers for the treatment of COVID-19 associated CRS.

The major advantage is that this would be easy to administer and relatively cheap and could be targeted to those patients who have either increasing cardiac symptoms (seems to be associated with the terminal event) or progressive pulmonary decline or findings.

One caveat regarding this approach is that JAK1/2 inhibitors will potentially block interferon-gamma signaling (and IL-6 signaling).

T cell production of Interferon-gamma has been associated with enhanced clearance of viral infections in mouse models. So, this may best be used for the treatment of the end stage CRS phase of COVID-19 as opposed to early use in asymptomatic or minimally symptomatic COVID-19 patients where there is a possibility of limiting innate antiviral responses that may aid in clearing the virus.

This approach could be considered in moderately symptomatic patients in conjunction with some effective antiviral therapy which does not currently exist. If better preclinical mouse models or viral induced ARDS/CRS existed and especially if quantitative RT-PCR for COVID-19 was available then early interventions with inhibitors of interferon-gamma signaling could more safely be tested.

We and a group from Ohio State (Goldsmith et al. Blood Adv, 2020 and Ahmed et al. Lancet Oncol, 2019) have shown that one JAK1/2 inhibitor, ruxolitinib, is extremely effective in blocking life-threatening CRS in patients with severe secondary HLH, and it is likely it would also be very effective in COVID-19 associated CRS and potentially reduce deaths, especially if viral replication and viral clearance is not impaired.

**Ascierto:** Preliminary experience from Xu et al clearly indicate that tocilizumab is an important tool against COVID-19 respiratory distress

**Cron and Chatham:** There are reports of favorable responses to tocilizumab when used as part of the treatment of critically ill COVID-19 patients in China. There are numerous case reports/series of patients with CSS associated systemic JIA or adults Still's disease respond-

ing favorably to tocilizumab (probably more experience with IL-1b inhibitors such as anakinra/rhIL-1ra in this setting)

**7. How would you formulate the clinical trials questions and how would you go about getting the answers? Are you aware of any clinical trials relevant to these questions?**

**DiPersio and Ghobadi:** Vaccines should be used as preventive strategies.

Infusion of anti-COVID-19 serum of antibodies against COVID-19 could be used early in the infection of anti-viral agents should be tested early after documented infection. A validated quantitative test such as qRT-PCR (does not exist to my knowledge) measuring viral loads would be key to evaluating the benefit of these.

Agents like IL-R, IL-6, IL-RA and JAK inhibitors could best be used late during the severe CRS phase.

Finally, those older patients with progressive disease and or new cardiac symptoms would be the best candidates for these interventions to reduce death.

**Ascierto:** In Italy at the moment is ongoing a large multicenter, open-label, phase II study with tocilizumab in COVID-19 pneumonia.

**Cron and Chatham:** The critical questions are:

**1. How are patients who are developing CSS best identified?**

Studies to assess markers of CSS sequentially in patients admitted with COVID-19 infection are needed to determine how to best identify early patients infected with COVID-19 who will develop CSS

**2. Can early intervention in such patients forestall development of severe respiratory dysfunction in COVID-19?**

Early intervention trials are needed, not just trials of patients who are critically ill—our experience in CSS occurring in other settings is that the earlier we intervene, the better the outcome.

**3. What interventions are most effective?**

Randomized controlled trials are necessary to confirm the effective interventions.

These are planned/underway with inhibitors of IL-1b (anakinra), IL-6 (tocilizumab), and anti-IFN $\gamma$  (emapalumab).

**8. What can be done now to get these questions answered ASAP?**

**Ascierto:** The ongoing phase II trial, and data coming from the observational study in Italy (hundreds of patients were treated in a real world experience) will give us a lot of information

**Cron and Chatham:** Funding of the needed clinical studies/trials. Rapid dissemination of interim results.

**9. Is there anything we've missed? I am sure there is a lot.**

**Ascierto:** All anti-IL-6 could potentially get the same results of tocilizumab ... sarilumab and others.



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Curigliano spoke with  
Alexandria Carolan, a reporter  
with The Cancer Letter.

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CONVERSATION WITH  
THE CANCER LETTER

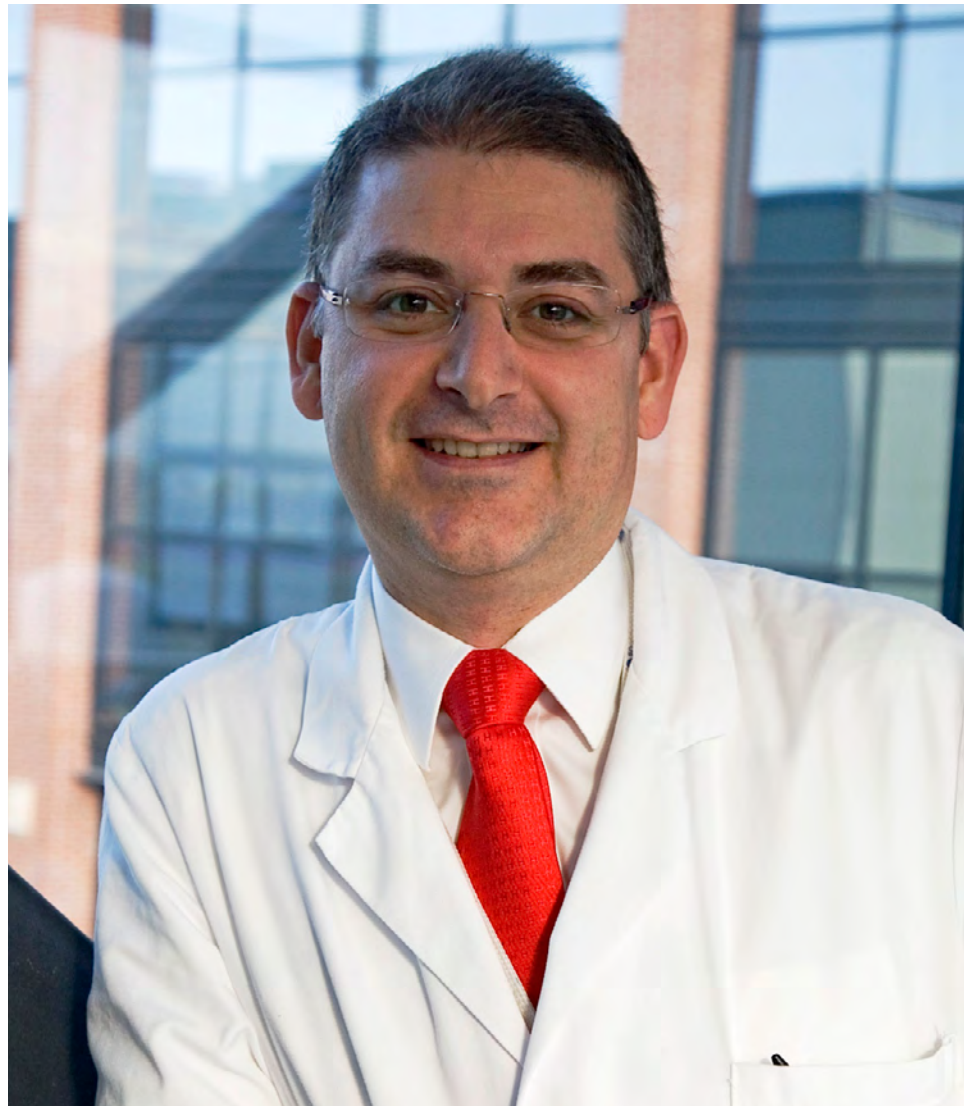
## Curigliano: Italy's COVID-19 cases keep rising; maybe next week the curve will flatten

**6,205 health professionals have tested positive and 44 have died**

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We have 6,205 medical doctors who are positive for coronavirus. It means that some of the people infected are health professionals. It's important to reinforce the message that we should protect ourselves.

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**Giuseppe Curigliano, MD, PhD**

*Associate professor of medical oncology, University of Milano;*

*Head, Division of Early Drug Development, European Institute of Oncology, Italy*

Week after week, Giuseppe Curigliano is waiting to see the first signs of a slowdown in Italy's cases of COVID-19, and week after week, he is disappointed.

We've been reaching out to Curigliano regularly:

- What to expect: Oncology's response to coronavirus in Italy (*The Cancer Letter*, [March 11](#)).
- Curigliano: "I don't want to see more people dying" (*The Cancer Letter*, [March 20](#)).

"The curve is quite clear that we are not in the condition to say it's flattened, maybe it's going to be flattened. I believe, by the weekend, maybe, we will have those data," Curigliano, associate professor of medical oncology at University of Milano, and head of the Division of Early Drug Development at the European Institute of Oncology, said to *The Cancer Letter*. "I hope to have a normal situation by the end of May, realistically."

Curigliano spoke with Alexandria Carolan, a reporter with *The Cancer Letter*.

Alex will keep checking in.

**Alex Carolan:** How have you been? How are things in Milan?

**Giuseppe Curigliano:** We are still not in the condition to say that we've flattened the curve. I can share my screen and I can show to you the data of today,

Sure.

**GC:** Just to show what is going on in Italy, we have 80,539 positive patients, and the total number of people who died are 8,165 as of March 26. If you look here, the curve is quite clear that we are not in the condition to say it's flattened, maybe it's going to be flattened. I believe, by the weekend, maybe, we will have those data.

The most important information that I can share with you, is that up to today, 44 medical doctors died due to COVID infection. Many of them are family doctors—44. Then, we have 6,205 medical doctors who are positive for coronavirus. It means that some of the people infected are health professionals. It's important to reinforce the message that we should protect ourselves. In the hospital, we are more protected, but family doctors, maybe, are not protected.

In the last week, we have the data of cancer mortality rate—those are the official data.

The median age, finally, of our population was 70 years old, or older, of the people who died in Italy. Twenty percent of them had active cancer. It means that out of the people who died, 20% of them are with active cancer, or a new diagnosis of cancer, or a cancer under treatment with any type of therapy.

Now, we are going to look into the case of those data. Important information is that 70% of Italian patients who died are men, and just 30% are women. In our country, we have less women patients with COVID infection. It is important information, I believe. We don't know why.

Maybe women in Italy underwent more vaccination in the past, because when a woman should plan a pregnancy, usually they test for all the type of infection. If they have no protection for a specific

agent, they receive a vaccination. This can be an explanation. We don't know. But for sure, we have less women infected. Really, we expect, the 70% is completely different.

So, 20% of those who have died of COVID in Italy were patients with cancer?

**GC:** With cancer, yes. These are confirmed data. Yes.

You said last week that you were treating three patients with cancer who also had COVID. Is this still the case?

**GC:** No, we have more patients now.

Last week, there were three. Now, in my hospital, we have eight patients with COVID.

You should consider that in my center, what we are doing, is having two checkpoints at the main entrance. The first one, is in order to understand if a patient has fever or not, and an evaluation of the anamnesis.

And, then there is a second one internally, where we complete a medical checkpoint. We are trying to reduce the number of infected people.

But, all the eight people that are positive entered the hospital without fever. They started treatment, and the day after, or two days after, they developed fever. We tested, and they weren't positive for COVID-19.

It seems that we may have patients with no symptoms that enter the hospital. Maybe they were positive, and then they developed symptoms after we started treatment. This is more complex, because if they received surgery, or they received the chemotherapy, then you have a patient with complications of COVID infection after receiving an active treatment.

**What happens in that case? How do you treat them?**

**GC:** Well, in that case, we isolate them. We intensified the monitoring, because this is very important. If fever is more than 39 degrees, they should be hospitalized. But if they have fever 37, 38, and they don't have or experience symptoms, you dismiss them, because there is the risk of infecting other patients, and we do close monitoring at home.

We've dedicated now, an area of the hospital for COVID patients—it is a limited area—six beds with trained staff. We have a trained nurse staff and trained doctor staff. Until now, this hospital had just one patient utilize it. This is a head-and-neck patient who received a major surgery, and who developed the symptomatic COVID-19 syndrome—and actually he's still hospitalized, is not intubated, and it's going well.

**How many of your own patients have COVID?**

**GC:** Now there are four. Four of my patients.

**Given that patients with COVID-19 were able to enter the hospital despite checkpoints—because they didn't have symptoms yet—are you changing how this system works? I mean, I know it's complicated.**

**GC:** What we are doing now is restricting access to the hospital for relatives. If you open the hospital during the visiting hours to relatives who potentially are infected, this may impact on your patients. No relatives can enter the hospital, no vendors—the hospital is open just for patients who should receive treatment.

This, psychologically, is quite stressful for patients, because, if you think about patients who are stressed because they have to receive a major surgery—and no relative can come in the hospital.

But, we have to protect them. They are not complaining. They understand, and they use much more FaceTime to communicate with their relatives. It's the only way to communicate.

**One other thing I'd like to discuss is the app you talked about last week, on how you're monitoring patients through that. Do you expect to use this app after the COVID-19 pandemic has passed? How will this change how you treat your patients?**

**GC:** I believe that remote monitoring with telemedicine or support of technology will be essential in the future.

Many visits can be really avoided. You can limit the access to the hospital, if you have to monitor toxicities that are expected, with drugs that you know.

If you know very well the safety profile of one agent, you should not ask the patient to come here every week to monitor toxicity. You can really use those apps or tele-monitoring to give more comfort to the patient, because accessing frequently to a hospital can be stressful for the patients.

I believe this will affect the way we treat them, and the standard of care of the patients.

I was discussing it this morning with my physician-in-chief, and he said, "Okay, now you are saying that you will do this- this-and-this after the COVID infection, but I am quite sure that in the future, everything will come back like in the past, because we never learn by the experience of the past stuff."

I hope he's mistaken, but I will try to change something after this pandemic, because we need change overall in the world. Something should change.

**What else do you think will change? What will be different?**

**GC:** This will change the way we do meetings. We organize every year meetings with 40,000 to 50,000 people just to do a discussion, to see the data live. But, I believe that maybe one meeting per year is enough for any specialties—

and many other cancer meetings can be delivered with streaming.

If you have some old meetings that are disease-oriented, maybe you don't need to do a usual thing. You can also go by streaming. I believe meetings are important for networking, but in terms of access to education, you can really do this by web.

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It seems that we may have patients with no symptoms that enter the hospital. Maybe they were positive, and then they developed symptoms after we started treatment. This is more complex, because if they received surgery, or they received the chemotherapy, then you have a patient with complications of COVID infection after receiving an active treatment.

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Also, medical education should change. I work in the University of Milano, and after the locking-down, you cannot take

lectures directly with students. We use streaming and Zoom meetings, exactly like you. All the students are connected, and they raise their hand or they ask questions—exactly the same thing. I know it's not exactly the same as doing training on the patient, but maybe for some lectures, you can deliver lectures online.

This will change. We should change this. This will impact patient care—implementing telemedicine—but also education and training—implementing streaming meetings. And when you have to do advisory boards or to discuss a steering committee, you don't need to do face-to-face meetings. You can really do everything by streaming, all these small meetings.

In the past, I was a frequent flyer. Two intercontinental flights per month, something like five or six flights in Europe, and then many flights to Italy. Now, I stopped any type of flights, and we did exactly the same meetings. So, we meet for nothing. With the exception of meetings that are larger—all the other meetings, we did them by streaming. It's very easy to do this.

As you know, you cannot bring 40,000 people together with the risk of any pandemics. We have to expect every three or five years the potential of a new virus spreading. We have to be ready first. We have to lock down after the first infection, or infected people. And we also have to think of a way to revise these huge meetings. It's very important, I believe, to think about this—because, maybe, in the future, we will save a lot of money that can be reinvested. There are activities, web activities.

**Do you think that COVID-19 has taught us how to respond to pandemics better in the future?**

**GC:** Yes, absolutely. I remember with SARS and MERS, if you remember it, you were very young. For SARS, AACR in Toronto was canceled.

But during SARS, a few thousands of people died. And I don't remember a general lockdown outside the Middle East. In the Middle East, there was a general lockdown, but in Europe, in the United States, we did not make that decision.

But now, with COVID-19, that was much more dangerous in respect to SARS. And, looking at the data on mortality, all around the world, people—in New York City—we have to learn from these experiences that we have to be prepared for another potential infection, and we have to be trained in those sort of things and all their potential infections.

We need to reserve part of our budget, to be an emergency plan. So, my suggestion is, every year, any hospital, also most hospitals, should have an emergency plan in case of a potential infection. And, so as we do training for fires, or for something like this, we also have to do training for a potential pandemic. This is my important message—any hospital.

**In the U.S., a lot of hospital systems are about to be very overwhelmed. One thing you mentioned earlier was how a lot of family medicine physicians are becoming infected in Italy.**

**GC:** 6,205 health professionals, with 44 doctors who died, many of them family doctors but also anesthesiologists, and infectious disease doctors. It's a lot.

In the United States, there's a shortage of personal protective equipment, and a lot of doctors are reusing them, or they're not able to access them, and their health care teams aren't able to access them. Was this the case at all in Italy, was this a problem?

**GC:** No, because we never experienced a shortage in our country, because since the beginning, we tried to buy, as a country, all available PPE across the world. In India, in China, in Turkey—we asked them for PPE. Despite *The Cancer Letter*, a few weeks ago, saying to be prepared.

The first thing to do in the United States, was to be prepared in terms of ventilators and personal protective equipment. I know many colleagues told us that they don't have personal protective equipment.

What we did in Italy was build the new factories. There was no factory in Italy producing masks, no factory in Italy! It's impressive.

We tried to build the same factories for using masks. It's important in the United States, to open, and to give facilities to factories that would like to produce masks, and all this type of protective equipment at a very low cost—so no one is interested in producing them.

That's why we imported from China and India. We imported all the masks from China and India, paying them a lot of money—because, now, the cost is very high.

In the U.S., they're trying to get the federal government to take action to have factories in the U.S. produce what is needed.

**GC:** Exactly. What we did in Italy. You need at least one week, but you can do this. It's like a war. This is a war economy. When you have to prioritize the factories who have to produce something you need, this is a war economy.

I'd like to bring this back to cancer patients. You talked about clinical trial disruptions last week. What are the disruptions, exactly? How is this affecting your own research?

**GC:** In the last two weeks, we generated more violations than in the last six months. Because, according to protocol rules, you should do CT scans, blood tests, exactly within the window of time that we did not respect. And, we did not respect this, because many patients have no access to hospitals. Many patients received scans at home, many patients received blood tests at home. Many patients missed visits that are required for the protocols.

And, we delayed these CT scans and blood tests. We delivered the drugs with specific delivery systems at home. For any one of these actions, that was a good action for the patients—it was a bad action for the protocol.

We generated protocol violations. And though the sponsors tried to face this emergency, some meeting protocol amendments, we generated violations now that, in a few weeks, will be no lon-

ger be violations, but will be new protocol rules.

There will be permission to do a CT scan at home, blood tests at home, to deliver the drugs at home.

Another important point was the use of enrollment. We had many patients coming to the hospital, and less patients enrolled in protocols, because we have to take care of the safety, so we did much more standard of care, and less enrollment. Many companies decided all over the world to stop accrual. Many big companies sent the letter to stop their accrual. This affected a lot of clinical trials.

Right. Do you think that this will affect cancer drug approvals in the future?

**GC:** Yes, I believe yes. Because if you have a registration trial for which you need to reach a target sample, if you stop for several weeks the accrual this will impact the delivery of the data. You will have less patients enrolled, a delay in the completion of the trial, a delay in the submission of the dossier to the FDA, and a delayed approval of a potential new agent. This is my impression.

How far into the future do you think that we'll see these disruptions?

**GC:** I believe, at least in my account, I hope the companies will consider this country by country.

I hope in Italy, to be realistic, by the end of May, to have exactly the same situation of the Wuhan Region, China. In this

weekend, they will reopen everything. I expect in my country to have flattened the curve by the middle of April, and then have a decrease by the end of April, and the complete reopening by the beginning of May or maybe mid-May.

In my country, I hope to have a normal situation by the end of May, realistically. We have to consider a delay of two weeks for France, Spain, and Germany, and the delay of three, four weeks for the United States. So, everything will be normal again across the Western seaboard, maybe for the end of July, realistically.

And not Easter, as Donald Trump said. Because he said that after Easter, everything will be reopened, and I don't think so.

**I think a lot of people in the U.S. agree. You expect to see that curve in Italy flatten in Italy by mid-April, now?**

**GC:** I hope that if we respect the social isolation and containment measures, I hope that for mid-April, we will have a decrease of infected people, exactly. Not a flatten of the curve, but a decrease. The flatten of the curve, I expect for mid-April.

**Are you still feeling positive, going forward?**

**GC:** I feel positive, because my family until now is safe. Because many friends of mine that are doctors are safe. I know of many colleagues who are medical oncologists that are in intensive care units. I know them, so I am worried about

those doctors that have been affected and have serious complications.

I really hope that there would be much more protection for family doctors, because the 44 doctors who died, are all family doctors—doctors who visit with patients with no protection, I assume, because they believed this was flu, and finally died due to complications of COVID-19.

**Could you describe what a family doctor is?**

**GC:** In Italy, we have a national health system for any single community, any single village or small town, has one to two family doctors that take care of basic medicine. All the family can go there to report the symptoms or any problem.

They decide if they give medication, and taking care of them at home or they can decide to send the patient to a specialist in a large hospital. You have to imagine that in the last six weeks, the first doctor that took care of all COVID patients on the frontline, was a family doctor. They were over there with something that was similar to flu symptoms in the beginning of January, and the family doctors had contact with them. The doctors there that are dying today have been infected three or four weeks ago, and they were not aware about COVID-19.

They have been at the front line. And actually, all the symptomatic patients at home, who have not been hospitalized, in a small town or in a small community, they are cured by the family doctors. They are the doctors they call—if they have an emergency, they go to their home. In Milano, we have thousands of family doctors, it's a huge city with millions of people.

**Are family doctors in Milan disproportionately affected?**

**GC:** Now we are trying to do more training for them and more education. Actually, Regione Lombardia is giving them personal protection equipment. Every week, they have to go in the central hospital to take personal protective equipment. We are reorganizing the network for them.

**Do you have anything else you'd like to add? General advice?**

**GC:** We expect from the United States of America, much more investment of research, and much more investment on delivering new clinical trials to take care of COVID patients. My request is to give a lot of interest to this COVID infection in order also to find something to cure those patients who can be cured. A huge investment from this.

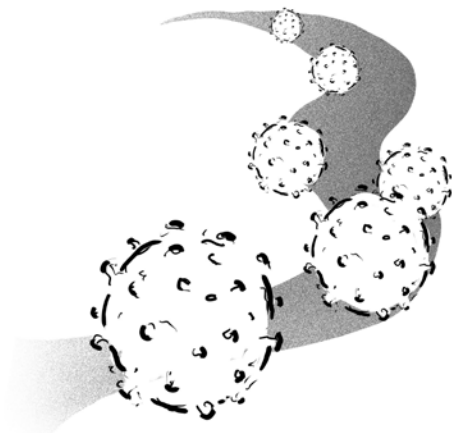
You have to take the leadership on this. OK?

**Agreed. Thank you so much, Giuseppe.**

**GC:** Thank you to you.

**Let's touch base again next week.**

## COVID-19 UPDATES



## ASCO 2020 annual meeting goes virtual

The annual meeting of the American Society of Clinical Oncology will go virtual this year, the society announced March 24.

“As public health safety measures related to COVID-19 extend, the ASCO board has concluded that the annual meeting, scheduled for May 29-June 2 in Chicago, cannot occur in person as planned,” ASCO said in a statement.

“That is why we still intend to deliver the latest cancer science to the global community during the annual meeting timeframe using a virtual format that respects the contributions of the authors and the work of the Scientific Program Committee,” the statement said. “Information on the format, dates, specific content, registration, refunds, and many other details will be available in the coming weeks and posted on [am.asco.org](http://am.asco.org).”

Abstracts will be published online and in the *Journal of Clinical Oncology*, though ASCO’s educational program will not

take place within the virtual annual meeting setting.

“As we confront this extraordinary situation, the health and safety of members, staff, and individuals with cancer—in fact, the entire cancer community—is ASCO’s highest priority,” Richard L. Schilsky, executive vice president and chief medical officer of ASCO, wrote a guest editorial in *The Cancer Letter* March 18 (*The Cancer Letter*, [March 18](#)).

ASCO’s statement on its virtual annual meeting is posted [here](#).

## Congress passes coronavirus relief bill, slating \$4.3B for CDC, \$3.5B for BARDA, \$945M for NIH, \$80M for FDA

The House of Representatives March 27 passed a \$2 trillion coronavirus relief package to “prevent, prepare for, and respond to coronavirus, domestically or internationally.” The bill appropriates pandemic response funds in the following amounts: \$4.3 billion for CDC, \$945.4 million for NIH, \$80 million for FDA, and \$200 million for CMS.

The Senate voted to approve the legislation 96-0 on March 25. President Donald Trump is expected to sign the bill immediately. The Coronavirus Aid, Relief and Economic Security (CARES) Act is the largest economic stimulus measure to date in U.S. history.

The bill provides \$3.5 billion to the Biomedical Advanced Research and Development Authority “for necessary expenses of manufacturing, production, and purchase ... of vaccines, therapeutics, diagnostics, and small molecule active pharmaceutical ingredients, including the development, translation, and

demonstration at scale of innovations in manufacturing platforms.”

Here’s a breakdown of the allocations by agency, institute, and program:

### Centers for Disease Control and Prevention: \$4.3 billion

- \$1.5 billion for states etc. to “carry out surveillance, epidemiology, laboratory capacity, infection control, mitigation, communications, and other preparedness and response activities”
- \$500 million for “global disease detection and emergency response”
- \$500 million for “public health data surveillance and analytics infrastructure modernization”
- \$300 million for the Infectious Disease Rapid Response Reserve Fund

### National Institutes of Health: \$945.4 million

- National Institute of Allergy and Infectious Diseases: \$706 million, of which \$156 million is allocated for “vaccine and infectious diseases research”
- National Heart, Lung, and Blood Institute: \$103.4 million
- National Institute of Biomedical Imaging and Bioengineering: \$60 million
- National Center for Advancing Translational Sciences: \$36 million
- Office of the Director: \$30 million
- National Library of Medicine: \$10 million

### Food and Drug Administration: \$80 million



- Salaries and Expenses: \$80 million, including funds “for the development of necessary medical countermeasures and vaccines, advanced manufacturing for medical products, the monitoring of medical product supply chains, and related administrative activities.”

### Centers for Medicare and Medicaid Services: \$200 million

- Program Management: \$200 million, of which \$100 million is allocated for the survey and certification program and prioritizing nursing home facilities in localities with community transmission of coronavirus

### Substance Abuse and Mental Health Services Administration: \$425 million

- Health Surveillance and Program Support: \$425 million

## NCI on the state of clinical trials, funding

The following are statements from NCI on the state of [clinical trials](#) and [funding](#) during the COVID-19 pandemic.

“Cancer patients are particularly vulnerable to infectious diseases such as COVID-19, both because of their underlying health condition and because cancer treatments can suppress the immune system. At this time, we do not know how the COVID-19 pandemic will evolve or the extent to which it will place stress on cancer patients, their families, and their caregivers.

“The Centers for Disease Control and Prevention and other public health experts have provided authoritative advice on how individuals can protect themselves. Patients should seek advice from their health care providers regard-

ing their individual care and whether they should be tested for COVID-19.

“A patient’s health care team is best suited to evaluate that individual’s unique situation and advise on the safest course of action. As more information becomes available on mitigation strategies from physicians caring directly for cancer patients, that information will be shared broadly in the oncology community. For example, researchers at the Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, and the University of Washington have published information about managing cancer care during the COVID-19 pandemic, and NCI is closely monitoring the clinical experience of cancer caregivers across the world.

“For individuals undergoing treatment for cancer, the spectrum of acute need for cancer treatment is broad. In some situations, it is essential that patients receive treatment immediately for their cancer. In other situations, such as for patients who are not receiving active treatment, visits for follow-up cancer care may be safely delayed. Patients should discuss individual treatment plans with their health care team.

“During the challenging situation of the COVID-19 pandemic, we understand that health care system resources will be limited, and this may affect cancer clinical trial operations. We do, however, believe that there are circumstances (e.g., in order to access potentially life-saving therapy) where patients with cancer should enroll or continue to participate in a clinical trial. Advice given to patients participating in clinical trials should be tailored to the individual patient based on their clinical circumstances.

“On March 18, the Food and Drug Administration issued guidance on the conduct of clinical trials of medical products during the COVID-19 pandem-

ic. In addition, NCI has provided guidance for clinical trials’ activities during the COVID-19 pandemic, with the intent of giving greater flexibility to the patient and their caregiver so that they may more easily be treated on a clinical trial if indicated.

“We continue to closely monitor NCI-supported clinical trials to help address the needs of investigators to implement accommodations so that they can, to the greatest extent possible, maintain continuity of care for their patients who are being treated on trials. If a clinical trials site’s policies and practices vary from the guidance we have outlined, they are encouraged to contact NCI’s Cancer Therapy Evaluation Program.”

## NCI’s Sharpless vows to support extramural research through crisis

NCI Director Ned Sharpless issued a statement outlining NCI’s strategy for responding to the COVID-19 pandemic:

“As we understand so well, biomedical research improves public health through scientific discovery. The COVID-19 pandemic only reinforces the importance of our work and the work of so many others who are dedicated to protecting and improving public health. I want to assure you that NCI, in partnership with NIH, is taking affirmative steps to support the extramural cancer research enterprise during this challenging time.

“I encourage you to read the recent post on NIH’s Open Mike blog about NIH operations during this public health emergency. NIH has established a comprehensive resource with guidance for grant applicants and funding recipients on NIH grant operations. I also recommend checking this resource often over

the coming weeks, as additional notices will be posted on a regular basis.

“At NCI, we are committed to sustaining progress against cancer, now and always. With this commitment in mind, earlier this month I asked NCI Principal Deputy Director Doug Lowy, M.D., to lead an NCI task force with a broad mandate, which includes maintaining the continuity of NCI operations during this public health emergency, including operations that support NCI extramural research.

“I am also deeply involved, working with other NIH institute directors and our colleagues at the Department of Health and Human Services as we respond to evolving developments related to COVID-19. NCI employees continue to work, many teleworking from home, to sustain our interactions with the extramural community.

“With that background, let me share a few updates on NCI extramural operations given the rapidly evolving situation we are witnessing.

“The NCI Division of Extramural Activities will ensure that all previously scheduled peer review meetings proceed using one of three alternate meeting formats that NIH identified: telephone-assisted, virtual, or video-assisted. Reviewers can find more information on these formats on the NIH Tools and Technology web page.

“If you are participating in the peer review of applications submitted to NCI, we ask you to please be flexible about the scheduling and the meeting format so that incoming applications can continue to be reviewed in a timely way.

“Once peer review is complete and grant applicants have access to summary statements, applicants should contact the appropriate NCI program director. Applicants will find contact information

for the program director in the top left corner of the summary statement.

“If you are not sure whom to contact, the appropriate contact for your application can be found on our Grants & Training webpage.

“If you have questions regarding grant applications you submitted, please pose your questions through eRA Commons.

“The NCI Office of Grants Administration continues to issue grant awards, revisions, and post-award actions. NCI staff will be following the NIH guidance on coronavirus administrative flexibilities related to grant awards.

“If you have questions about your awarded grant, please contact the grants management specialist listed on your Notice of Award. If you aren't sure who your assigned specialist is, please visit Grants Management Contacts on our Grants & Training webpage.

“Although we are facing truly exceptional circumstances, in the United States and globally, I am confident that we will weather this crisis together and grow stronger as an international cancer community. And let me also express my heartfelt gratitude for your continued dedication to your work and our nation's health during these trying times.”

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## **AACI urges immediate implementation of Defense Production Act**

The Association of American Cancer Institutes has urged President Donald Trump to invoke the Defense Production Act to forcefully confront the COVID-19 emergency.

The [letter](#), dated March 23, follows:

“Dear Mr. President:

“As the directors of 97 leading academic cancer centers in the U.S., we are responsible for treating a particularly vulnerable patient population. Many of our patients are immunosuppressed, and most have serious comorbidities. Consequently, they are particularly susceptible to having serious complications and poor outcomes from SARS-CoV2 infection (which causes COVID-19).

“In fact, some of our patients have already contracted this virus and died from respiratory failure. Furthermore, our patients generally require frequent interactions with health care providers, who are being increasingly affected themselves with COVID-19 or are being seconded to assist in the treatment of COVID-19 patients.

“Our physicians and advanced practice personnel are witnessing firsthand the increasing strain on our healthcare systems, most notably the widespread shortage of personal protective equipment, such as surgical and N95 masks, gowns, nasal swabs, and face shields, as well as advanced life support systems, such as ventilators and ECMO devices. In a word, the situation is already desperate in many of our hospitals, and rapidly edging towards utter disaster.

“For this reason, we implore you to immediately invoke and utilize the Defense Production Act to marshal the power of American manufacturing to address the COVID-19 emergency. We also request that you mobilize units of our military, such as the Army Corps of Engineers to aid in rapid construction of temporary hospital facilities and military medical personnel to assist and relieve our front-line emergency room and intensive care unit personnel.

“The full scope of this emergency is only beginning to be apparent, but it is already clear that there is not a second to lose. Failure to act decisively and im-

mediately will undoubtedly result in the tragic, massive, and ultimately avoidable loss of many American lives.

“Thank you very much for considering our request.”

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## Nebraska Medicine develops method to reuse personal protective equipment

In light of the national shortage of one-use personal protective equipment, Nebraska Medicine has developed a safe and effective method to decontaminate these items so they can be used multiple times.

A team led by John Lowe, UNMC assistant vice chancellor for inter-professional health security training and education, is using ultraviolet light towers to irradiate high numbers of masks, which were originally designed to only be used once. The strategy will allow Nebraska Medicine to greatly extend its supply of these items during the coronavirus pandemic.

“The shortage of PPE is a nationwide issue—each and every one of these items is increasingly precious,” Mark Rupp, chief of the infectious diseases division at UNMC, said in a statement. “Although we were well prepared, our supplies were beginning to dwindle. We had to find a way to keep our providers and patients safe, and this will definitely help us achieve that goal.”

The decontamination of these items works like this: groups of masks are safely bagged and transported to a room inside the hospital which is equipped with two ultraviolet light towers. The PPE is hung on wires stretching the length of the room and then decontaminated when the lights are powered on. The

items are then removed and returned to the original owners for reuse.

“The shortage has forced us to be innovative,” Lowe said. “While these items weren’t meant to be used more than once, this is a 100% safe way to extend their useful life. Other major hospital systems in the U.S. have also started to implement this method for the same reason we are.”

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## Nebraska Medicine infectious disease experts release open-access book on quarantine and isolation

Four University of Nebraska Medical Center physicians who also have roles in the Global Center for Health Security at UNMC/Nebraska Medicine, recently released an open-access book about quarantine.

The book, published before the onset of the coronavirus pandemic, is available through Amazon and the University of Nebraska Press.

“[Nebraska Isolation and Quarantine Manual](#),” the book, shares practical aspects of why, how and when to apply quarantine and isolation for conditions that warrant care in biocontainment or quarantine. It also includes the history of quarantine and its legal and ethical considerations.

The book was written and edited from lessons learned at UNMC during the West Africa Ebola virus outbreak.

The authors say the book is especially useful for medical, nursing and public health personnel who work in medical centers, clinics and in the community,

as well as for students in the health professions.

Ted Cieslak, Mark Kortepeter, Christopher Kratochvil, and James Lawler, co-edited the book. The book covers historical and legal aspects of quarantine and isolation on high-consequence infectious diseases that might be considered for specialized care in a biocontainment unit.

“Given our experience in managing Ebola during the West African outbreak, the fact that we possess the nation’s largest biocontainment unit, and we just opened the nation’s first (and only) federal quarantine facility, we felt that we possessed the unique expertise necessary to produce such a book,” Cieslak, medical director of the National Quarantine Unit at UNMC/Nebraska Medicine, said in a statement. “Despite the voluminous nature of the medical literature, we could find no other text designed to be a practical resource for clinicians, policy makers and public health officials in the field. We felt it was incumbent upon us to write one.”

“We had no idea how timely the book arrival would be, given the current COVID-19 pandemic. We are pleased this might be beneficial for medical personnel across the world in a time of need,” Kortepeter, professor of epidemiology in the UNMC College of Public Health, said in a statement. “There is not a lot of specific information about what diseases quarantine should and should not apply to, which is what makes this document even the more useful.”

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## NSGC urges Congress to recognize genetic counselors

Patients with Medicare and Medicaid coverage are unable to receive genetic counseling through telehealth, and The

National Society of Genetic Counselors is urging Congress to act.

The state of emergency caused by the COVID-19 pandemic is causing genetic counseling clinics to close down and convert to telehealth practices. At the same time, Genetic counselors are not recognized by Centers for Medicare & Medicaid Services, the society said.

NSGC asks that CMS waive the “incident to” requirement for genetic counselors, and allow certified genetic counselors to provide remote services by phone to Medicare and Medicaid beneficiaries.

NSGC is urging Congress to recognize genetic counselors under the Social Security Act, by enacting H.R. 3235. NSGC is requesting a Section 1135 waiver to ensure there isn't a disruption of these genetic services.

## Breast cancer patient featured in *The Cancer Letter* receives testing for COVID-19, awaits results

Last week, *The Cancer Letter* spoke with Janice Cowden, a patient with metastatic breast cancer and symptoms of COVID-19—who was denied testing despite being especially vulnerable to the disease (*The Cancer Letter*, [March 20](#)).

Cowden has since received two tests for COVID-19—a nasopharyngeal swab at a curbside clinic, and a throat pharyngeal swab at the office of her primary care physician. She has yet to receive the results of either test.

Prior to developing symptoms, Cowden had attended a fundraiser with about 300 people—including dozens of women with metastatic breast cancer.

## Resources/FAQs

### Federal government:

- **NCI Emergency Resources:** What people with cancer should know about the coronavirus
- **NCI guidance:** Interim guidance for patients on clinical trials supported by the NCI Cancer Therapy Evaluation Program (CTEP) and the NCI Community Oncology Research Program (NCORP).
  - ▶ [More from NCI: What people with cancer should know about coronavirus.](#)
  - ▶ [Coronavirus guidance](#)
- **FDA guidance:** Conduct of clinical trials of medical products during COVID-19 pandemic
  - ▶ [More FDA updates: Medical Countermeasures Initiative, on COVID-19](#)
  - ▶ [FDA continues to facilitate access to crucial medical products, Including ventilators](#)
  - ▶ [FDA provides update on patient access to certain REMS drugs during COVID-19 public health emergency](#)
  - ▶ [A message to patients with cancer and Health Care Providers About COVID-19](#)

### Professional societies:

- **American Society of Clinical Oncology FAQ:** Emerging issues and challenges in caring for patients with cancer during the coronavirus pandemic
- **American Cancer Society FAQ:** Common questions about the new coronavirus outbreak

- ▶ [ACS clinical guidance:](#) COVID-19 elective case triage guidelines for surgical care
- ▶ Create a [surgical review committee](#) for COVID-19-related surgical triage decision making

- **Society for Immunotherapy of Cancer Resources:** Patient management and basic and translational research
- **Community Oncology Alliance resources:** Coronavirus (COVID-19) practice resources and protocols
- **Leukemia & Lymphoma Society FAQ:** Resources and what you should know about the coronavirus
- **American Society for Radiation Oncology FAQ:** COVID-19 recommendations and information
- **American College of Surgeons resources:** For the surgical community
- **Society for Immunotherapy of Cancer resources:** Implications for patients, translational research
- **American Society for Transplantation and Cellular Therapy resources**
- **European Blood and Marrow Transplantation Society recommendations**
- **World Marrow Donor Association resources**

### Research centers:

- **St. Jude Children's Research Hospital FAQ:** COVID-19 and children with cancer
- **Journal of the National Comprehensive Cancer Network:** How to manage cancer care during COVID-19 pandemic

## IN BRIEF



## UCLA, UT Southwestern join NCCN

UCLA Jonsson Comprehensive Cancer Center and UT Southwestern Simmons Comprehensive Cancer Center are the newest members of the National Comprehensive Cancer Network.

Experts from both centers will now contribute to NCCN Clinical Practice Guidelines in Oncology.

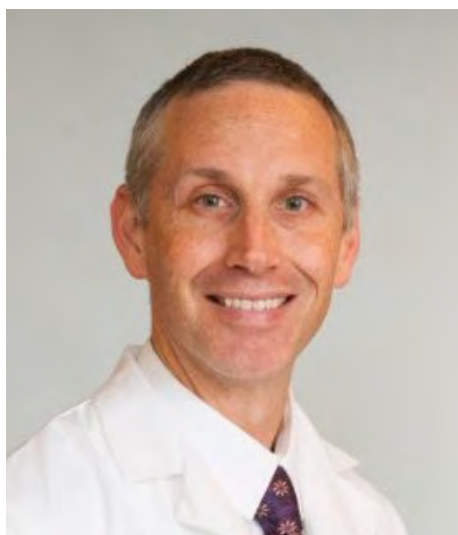
“We look forward to joining our peer institutions and bringing our focus on cutting-edge research and top-quality cancer care to this association of the nation’s top cancer centers,” Michael Teitell, director of UCLA Jonsson Comprehensive Cancer Center, said in a statement.

“We are excited to be able to join forces with the other leading cancer centers who are part of NCCN,” John Sweetenham, associate director of Clinical Affairs, UT Southwestern Simmons Comprehensive Cancer Center, said in a statement. “Working with the other member institutions, we will ensure that the best possible evidence-based cancer

care is available to patients throughout the nation and beyond. Our membership will bring the combined expertise of 30 elite cancer centers to the people of North Texas.”

In 2019, more than 1,500 experts from NCCN member institutions helped create and update NCCN Guidelines. Those guidelines provide the latest evidence- and expert consensus-based recommendations applying to 97% of cancers affecting patients in the United States, and also include prevention, screening, and supportive care topics.

## S. Michael Rothenberg joins Pfizer Boulder Research Unit



S. Michael Rothenberg has joined Pfizer as the head of Early Clinical Development at the Boulder Research Unit.

Prior to joining Pfizer, he was vice president of Research and Development at Loxo Oncology, where he led the overall clinical development of selpercatinib (LOXO-292, ARRY-192), a selective RET kinase inhibitor for patients with RET gene-altered cancers, and the early clinical development of LOXO-305, a next generation BTK inhibitor for patients with B-cell malignancies.

“We are very excited that Dr. Rothenberg has joined Pfizer as the head of Early Clinical Development for the Boulder research unit,” Nicholas A. Saccomano, chief scientific officer of Pfizer Boulder Research & Development, said in a statement. “Given his vast experience in medical oncology and developing targeted oncology agents, we have every reason to believe that his expertise will help Pfizer and the Boulder team bring breakthrough medicines to people living with cancer.”

While at Loxo, Rothenberg worked closely with the team at Array BioPharma, which became the Pfizer Boulder Research Unit after its acquisition in June 2019, on the preclinical development of selpercatinib and the next generation TRK kinase inhibitor LOXO-195. Prior to his work in biotechnology, he was a medical oncologist and cancer researcher at the Massachusetts General Hospital Cancer Center.

## Kathleen Goss named associate director for administration at University of Chicago Comprehensive Cancer Center

Kathleen Goss was named associate director for administration at the University of Chicago Medicine Comprehensive Cancer Center.

In this role, Goss has broad oversight for administrative and fiscal management of the comprehensive cancer center, including accounting and financial transactions, personnel, IT infrastructure to support clinical trials operations, pre- and post-awards for the Cancer Center Support Grant and multiple interdepartmental grants, cancer center public relations and communications, and philanthropic activities.

# THE CLINICAL CANCER LETTER



## TRIALS & TRIBULATIONS

### Against all odds

### Unrelated stem cell transplants in coronavirus times



**By Steven Devine**

*Chief Medical Officer, National Marrow Donor Program*



**Alexander Schmidt**

*Global Chief Medical Officer, DKMS*

The COVID-19 crisis has consequences not only for those who have become infected and the doctors and nurses who care for them. The care of other patients is also threatened by the increasing stress that national health systems and societies as a whole are under.

Also, cancer has no borders, and patients in need continue to need our help. Against all odds, we care for unrelated stem cell transplants in these

difficult times. As chief medical officers of the National Marrow Donor Program (NMDP) and German-based DKMS, the two world's largest volunteer bone marrow and blood stem cell donor organizations, for us safeguarding our donors is always our highest priority.

Currently, more than 37 million donors are registered worldwide. In 2019 alone we have been working closely together to get 1,734 international DKMS do-

nated stem cells for patients to the United States.

In times of COVID-19, several organizations have worked collaboratively to develop enhanced guidelines for the assessment of volunteer unrelated blood/bone marrow donors during the COVID-19 crisis to limit the risk both of viral transmission and any additional adverse events to the donors.

A question was raised in a recent issue of *The Cancer Letter* that perhaps a haploidentical related donor might be preferred, given all the uncertainties imposed by the current COVID-19 crisis (*The Cancer Letter*, [March 13](#)).

Yet, unrelated donor BMT remains the most widely used platform of allogeneic transplantation, with the largest body of evidence and the longest clinical follow-up.<sup>1</sup> Many retrospective observational studies have been published suggesting overall survival and other important clinical outcomes may be equivalent comparing matched unrelated donor to haploidentical donor transplantation.

These studies are important but are confounded and typically underpowered to detect clinically relevant differences.<sup>2</sup> The largest analysis performed to date concluded that absent a matched related donor, a matched unrelated donor remains the next best option for most patients.<sup>3</sup>

Today, general consensus is that if a well matched volunteer donor can be identified and made available in a reasonable time frame, that donor is preferred to a haploidentical related donor.

Since donor and patient should match their human leukocyte antigens (HLA) as closely as possible and the HLA system is extremely diverse, a large number of potential stem cell donors is needed.

Ultimately, decisions about the optimal donor are best made by the treatment teams at the transplant centers. Our goal is to help procure unrelated donor blood or bone marrow if that is the best choice for their patients.

We acknowledge the tremendous sacrifices our donors make when they consent to donate bone marrow or blood stem cells in an effort to save a patient's life. During the COVID-19 crisis, efforts to mitigate the spread of SARS-CoV-2 have imposed substantial travel restrictions

that the NMDP, DKMS and other registries have worked diligently to overcome.

Just over a week ago, the NMDP Patient Advocacy group worked tirelessly with US legislators and ultimately received a blanket travel ban waiver, almost certainly the only of its kind in the country, signed by the Director of the Centers for Disease Control and Prevention.

This ensures that European couriers can transport products into the US despite the travel ban. The waiver ban has been distributed to European embassies and US ports of entry, allowing non-US citizens to enter the US with donor products despite the travel ban.

In this chaotic situation, it is perfectly normal for transplant physicians and coordinators to wonder whether the stem cell product of an unrelated donor from another continent should really be the preferred therapy option for their patient.

Although there are concerns regarding donor availability during the COVID-19 pandemic: DKMS, thanks to the NMDP blanket travel ban waiver, signed by the director of the CDC, has transported 40 stem cell products from European DKMS donors successfully to the United States last week alone.

Each requested product could be delivered properly.

We know that further challenges are very likely to await in the coming weeks and months. It is reasonable to assume that passenger air traffic will be further reduced or stopped altogether. Preparations for this scenario are in full swing.

Together with highly dedicated airlines and courier companies, successful tests have already been conducted to transport the stem cell products in the cockpits of cargo planes without a dedicated courier. This process could perhaps become the new standard for the further course of the crisis.

In order to further ensure patient safety, most international registries are now strongly recommending that unrelated donor products be collected prior to initiation of patient conditioning. This will guarantee the donor graft is available on the intended day of transplantation.

In fact, the NMDP has just made cryopreservation prior to conditioning a requirement, and others may follow suit.

Collectively, the volunteer unrelated donor community, together with the transplant centers, is working collaboratively day and night to continue uninterrupted our commitment to connect these remarkable donors with their patients.

We are still receiving many requests for unrelated donor products, as transplant centers continue to believe this is in the best interests of their patients.

## References:

1. Fleischhauer K. Selection of matched unrelated donors moving forward: from HLA allele counting to functional matching. *Hematology Am Soc Hematol Educ Program.* 2019 Dec 6;2019(1):532-538
2. Shaw BE. Related haploidentical donors are a better choice than matched unrelated donors: Counterpoint. *Blood Adv.* 2017 Feb 14;1(6):401-406.
3. Shouval R, Fein JA, Labopin M, Kröger N, Duarte RF, Bader P, Chabannon C, Kuball J, Basak GW, Dufour C, Galimard JE, Polge E, Lankester A, Montoto S, Snowden JA, Styczynski J, Yakoub-Agha I, Mohty M, Nagler A. Outcomes of allogeneic haematopoietic stem cell transplantation from HLA-matched and alternative donors: a European Society for Blood and Marrow Transplantation registry retrospective analysis *Lancet Haematol.* 2019 Nov;6(11):e573-e584. doi: 10.1016/S2352-3026(19)30158-9.

## CLINICAL ROUNDUP



## Venclexta combination improves OS in previously untreated AML

The phase III VIALE-A study demonstrated that Venclexta in combination with azacitidine, a hypomethylating agent, showed a statistically significant improvement in overall survival in people with previously untreated acute myeloid leukemia who were ineligible for intensive induction chemotherapy, compared to azacitidine alone.

The trial, sponsored by Genentech, a member of the Roche Group, met its dual primary endpoints of overall survival and composite complete remission rate.

FDA previously granted Venclexta accelerated approval in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of people with newly-diagnosed AML who are 75 years or older, or for those ineligible for intensive induction chemotherapy due to coexisting medical conditions, based on response rates from the M14-358 and M14-387 studies.

Continued approval for this indication may be contingent upon verification

and description of clinical benefit in confirmatory studies. Venclexta has also been granted five Breakthrough Therapy Designations by the FDA, including two for previously untreated AML.

Venclexta is being developed by AbbVie and Genentech. It is jointly commercialized by the companies in the United States and commercialized by AbbVie outside of the United States.

## Intense form of radiation slows disease progression in some men with prostate cancer

Highly focused, intense doses of radiation called stereotactic ablative radiation may slow progression of disease in a subset of men with hormone-sensitive prostate cancers that have spread to a few separate sites in the body, according to results of a phase II clinical trial of the therapy.

The trial, called ORIOLE and led by Johns Hopkins Kimmel Cancer Center researchers since 2016, compared the effectiveness of SABR versus “wait and watch” observation in recurrent cases of oligometastatic prostate cancer.

“It has been a longstanding question, especially important now in the era of immunotherapy, whether any type of radiation, and SABR specifically, can stimulate the immune system,” study leader Phuoc Tran, professor of radiation oncology and molecular radiation sciences at the Johns Hopkins University School of Medicine and a member of the Johns Hopkins Kimmel Cancer Center, said in a statement. “Our trial offers the best data to date to suggest that SABR can cause a systemic immune response.”

Metastatic prostate cancer is incurable, and men with recurrent hormone-sen-

sitive cancers may prefer to delay one of the standard treatments, an anti-hormone therapy called androgen deprivation therapy.

A report on the study is available in the journal *JAMA Oncology*.

Among the 54 men enrolled in the trial, the disease progressed within six months in seven out of 36 (19%) of participants treated with SABR, compared to 11 out of 18 participants (61%) undergoing observation alone. The risk of new cancers at six months was also lower, occurring in 16% of those receiving SABR compared to 63% of those under observation.

There were no significant differences in clinically meaningful side effects or in reports of pain related to the treatment between the two groups, the study found. The average age of the men on the ORIOLE trial were 68-years old, and most participants were Caucasian.

Analysis of immune system white cells in blood drawn from the patients indicated that SABR treatment was associated with an expanded population of T cells, suggesting that the treatment stimulated a full-body immune system response to their cancers, Tran said.

Tran co-directs the Kimmel Cancer Center’s Cancer Invasion and Metastasis program with Andrew Ewald and Ashani Weeraratna, aimed at studying the process by which cancers spread, to expand and develop better treatments for patients with advanced cancers.

The findings suggest SABR might be usefully paired with other immunotherapies to treat recurrent oligometastatic prostate cancers, but Tran cautioned that any potential benefits of such combined therapy will need to be tested in future clinical trials.

The research team also detected a set of tumor mutations in genes known to be



important for suppressing cancer development in some patients that correlated with a higher risk of cancer progression even among those undergoing SABR.

“This may be a molecular signature which is indicative of the underlying biology of the patient’s cancer,” Tran said.

The biomarker could help clinicians know “which patients are going to benefit the most from a metastasis-directed therapy like SABR” compared to a systemic treatment such as chemotherapy,” Tran said.

The ORIOLE results also suggest that SABR treatment may remove or affect signals that promote the development of micrometastases in recurrent oligometastatic prostate cancer, rather than just “resetting” the clock on the disease until metastases grow large again, said Tran.

Tran and team will continue with phase II studies to determine if they can increase the number of participants with slower disease progression. In the ORIOLE trial, patients with metastatic lesions in the bone were most likely to have their cancers recur in a new bone site. To target these new metastatic bone lesions, Tran and colleagues have another clinical trial called RAVENS that combines SABR with radium-223 (Xofigo) that targets metastatic cancer in the bones.

## Repurposed antidepressant may be a treatment option when prostate cancer comes back, USC study finds

An antidepressant in use for decades, repurposed to fight prostate cancer, shows promise in helping patients

whose disease has returned following surgery or radiation, a pilot study at USC shows.

Phenelzine, a MAO inhibitor, represents a potential new treatment direction with fewer side effects for men with recurrent prostate cancer, researchers said.

“To our knowledge, this study is the first clinical trial of an MAO inhibitor in cancer patients,” senior author Jean Shih, a University Professor in USC’s School of Pharmacy who has studied the enzyme MAO, or monoamine oxidase, for four decades, said in a statement.

The research appears in *Prostate Cancer and Prostatic Diseases*.

“If our findings are confirmed, this could be part of a new avenue for patients that could avoid undesirable side effects of standard therapies,” first author Mitchell Gross, a medical oncologist and research director at the Lawrence J. Ellison Institute for Transformative Medicine of USC, said in a statement. Gross and Shih have been collaborating for several years to bring her research out of the lab and into the clinic.

In the study, 11 of 20 participants had a measurable decline in their PSA levels after 12 weeks of twice-a-day treatment, with the greatest decline in PSA being a 74% drop.

In prostate cancer, MAO inhibitors disrupt androgen receptor signaling — the main growth pathway for prostate cancer. Previous studies with animals and human prostate cancer cell lines showed that MAO inhibitors decreased the growth and spread of prostate cancer, the researchers found.

Because the MAO inhibitor phenelzine is already FDA-approved, the researchers were able to rapidly design and implement a pilot study to test the drug’s ability to fight cancer.

For this study, researchers enrolled 20 participants who had been treated for prostate cancer and who had elevated PSA levels. Patients received the MAO inhibitor phenelzine twice a day for 12 weeks. Fifty-five percent of the men experienced PSA declines; five of them saw PSA level declines of 30% or more; two participants saw decreases of 50% or more.

Three patients had to drop out due to dizziness or hypertension.

The main limitations of the study include the lack of a placebo comparison group and the small sample size, researchers said. Additional studies are planned.

## INSTITUTIONAL PLANS

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