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MaineHealth Physician Recruitment Center



Associate Medical Director, Medical Oncology/Hematology and Cancer Genetics

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For more information, please contact Gina Mallozzi, Physician Recruiter at (207) 661-2092 or gmallozzi@mainehealth.org.

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I am certain that our subscribers will agree that our coverage of COVID-19 should be widely available. Making it open-access is consistent with best practices in journalism today.

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We are in this together

Dear Reader,

As the leading independent source of news in oncology, *The Cancer Letter* has decided that it is our moral imperative to provide coverage of COVID-19 free of charge until this crisis is resolved.

Our colleagues at other premier news publications and scientific journals, too, are removing paywalls on material related to the pandemic.

This is clearly the right thing to do for you, our readers, the courageous people on the front lines.

Through our award-winning investigative reporting, through conversations with leading experts, and through guest editorials from leaders in oncology, *The Cancer Letter* will continue to explore how COVID-19 affects our unique readership.

This coverage of COVID-19 is now consolidated on one [landing page](#).

Even amid the pandemonium, we can see that cancer scientists and clinicians stand poised to play key roles in finding effective treatments for this disease. Oncology has built a unique clinical trials infrastructure capable of generating answers rapidly and reliably. Oncology, immunology, and rheumatology have been crossing paths for decades, and now they intersect in a manner never seen before.

In years to come, COVID-19 will redefine medicine—including oncology—and *The Cancer Letter* will be there, providing reliable, authoritative information about events affecting you and the world we live in.

I am certain that our subscribers will agree that our coverage of COVID-19 should be widely available. Making it open-access is consistent with best practices in journalism today.

Our ongoing reporting on oncology issues that brought you to us will continue, and, as this crisis unfolds, we will place this content back behind the paywall. *The Cancer Letter* is now in its 46th year of publication, and we will be here for decades to come.

Taking down the paywall for our COVID-19 coverage is not something we take lightly. Over 90% of *The Cancer Letter's* revenues come from subscriptions, less than 10% from advertising, and only a fraction of advertising comes from pharmaceutical companies. Subscribers like you keep our lights on. I hope you will support our ongoing coverage:

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For a short time, we are offering 15% off on all advertising to any subscriber of *The Cancer Letter*. Our readership numbers have doubled in recent months. Now is the time to advertise your job openings, virtual meetings, and more. We will honor this rate for any ads purchased between now and April 30; however, you are free to schedule those ads beyond that date. Please download our [media kit](#) and contact katie@cancerletter.com to learn more.

New coverage and submission guidelines

The Cancer Letter's coverage of COVID-19 is consolidated on this [landing page](#), which we will continue to update as this crisis unfolds.

If you would like to be notified of new issues and special reports, please join our [mailing list](#). We also post about our latest stories on [Twitter](#).

In addition to our in-depth reporting on COVID-19 issues, we have also expanded our news briefs to include a section exclusively devoted to COVID-19 news.

The Cancer Letter is accepting submissions of:

- **Press releases related to COVID-19 and cancer.** To submit, please add news@cancerletter.com to your distribution list.
- **Guest editorials and commentary.** To inquire about submissions, please contact me directly at paul@cancerletter.com. Big ideas and rough drafts are welcome.

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GUEST EDITORIAL

FRIENDING VIRAL FOES: THE ZIKA STORY AND (PERHAPS) LESSONS FOR COVID-19

On a recent call with directors of cancer centers, NCI Director Ned Sharpless reminded us that quarantines present opportunities for scientists to think deeply.



By Scott M. Lippman, MD

*Director, Moores Cancer Center;
Distinguished Professor of Medicine, Chugai Chair;
Associate vice chancellor Cancer Research and Care,
University of California, San Diego School of Medicine*

Ned illustrated his point with an example from outside the cancer field:

In 1665, a college kid named Isaac Newton was sent home from Cambridge to go into social isolation for what became known as the Great Plague of London. He returned to Cambridge a bit more than a year later, bringing back the foundations of calculus, his theory of optics and, depending on whom you talk to, the theory of gravity.

Although our time is different from Newton's, under normal circumstances, today's scientists are swamped,

performing or overseeing day-to-day experiments, mentoring, teaching, grant-writing, and traveling to conferences, all of which doesn't leave much time to pause, reflect deeply on our results and place them in a larger context of biology and medicine.

Today's COVID-19 pandemic urges us to think big.

As cancer scientists, we find ourselves at a cross-section of oncology, rheumatology and infectious disease. They haven't merged into a monolithic science, and may not need to, but more than ever, we

are finding these three disciplines at the same intersection. Call it the COVID-19 Interchange.

[A related commentary by cancer immunologist and "Checkpoints" lead singer Rachel Humphrey, head of R&D TIO Bioventures Discovery Engine and chief medical officer, Treadwell Therapeutics, appears on [page 9](#).]

As cancer people, we have developed an institutional infrastructure—the NCI-designated cancer centers, the national clinical trials infrastructure—that's unique in medicine. And, for a

long time now, oncologists, drug developers and the FDA have been speaking the same language. If we are able to maintain our cool heads even as the world around us continues to crumble under the onslaught of COVID-19, we will be able to answer questions quickly—and to produce transformative science.

As director of a cancer center, I remind myself that this is the challenge all of us trained for, this is the infrastructure we built. This infrastructure took a long time to build. In an [oral history](#) in 1997, former NCI Director Vincent DeVita said he regarded the institute's Viral Cancer Program as “one of the greatest contributions to science.”

At the time, DeVita said that he counted seven Nobel Prizes that are attributable to the program. Without bean-counting the Nobels, let's just say that, surely, there have been others since.

DNA viruses such as HBV and HPV are well known for their roles in cancer development, and interplay with RNA viruses and cancer. For example, HIV retrovirus infection leads to compromised immunity and with DNA viruses, cause Kaposi's sarcoma, aggressive B-cell lymphomas, and cervical cancer.

Importantly, the cytokine release syndrome, seen in several viral diseases, was observed as an adverse event in CAR T-cell therapy and managed with a drug approved in rheumatology. Drugs that were used to control CRS in the CAR T-cell setting are now being tested in COVID-19 ([The Cancer Letter, March 27](#)).

Listening to Zika

While viral epidemics pose severe challenges to society, there are instances where thoughtful efforts can turn these foes into potential friends in the fight against cancer. This is also a case study in thinking deeply, following sci-

entific leads, breaking silos—and just sheer luck.

I believe that in the midst of COVID-19, and based on this conceptual background, it may be informative to consider the 2015-2016 viral outbreak—the case of Zika virus.

Zika virus was initially isolated in 1947 from a monkey in the Zika forest of Uganda, followed by identification in mosquitos in the same area, leading to its naming—only later skipping species to humans. ZIKV infection was initially thought to cause a self-limiting and mild febrile disease—until a widespread epidemic of Zika virus (ZIKV) infection was reported in 2015 in South and Central America and the Caribbean.

While infected individuals can often be asymptomatic or have only mild symptoms, of mounting concern were reports linking ZIKV infection to fetal and newborn microcephaly.

This devastating viral outbreak stimulated remarkable research first reported in 2016 is uncovering Zika mechanisms that may allow scientists to turn this viral foe against babies into a cancer foe against stem-cell mediated drug resistant mechanisms.

One day after a report, led by Florida State University researchers showing that Zika virus infects and kills neural precursor cells (i.e. neural stem cells and neural progenitor cells), a postdoctoral fellow, Zhe Zhu, in the laboratory of Jeremy Rich, who at the time was at Cleveland Clinic, hypothesized that Zika could be useful in targeting drug-resistant cells within glioblastoma, the cancer stem cells, which share many characteristics with neural progenitor cells.

Rich is now a professor at the Department of Medicine, Neurosciences, and director of the Neuro-Oncology and Brain Tumor Institute at UCSD Moores Cancer Center.

In today's science, Eureka moments are documented in emails. Here is Zhe Zhu's:

From: Zhu, Zhe
Date: Thu, Mar 31, 2016 at 1:17 PM
Subject: ZIKA VIRUS in glioma stem cells
Cc: Rich, M.D., Jeremy

Hi Jeremy,

There was two Cell stem cell paper coming out yesterday, I would like to discuss with you about Zika virus in glioma stem cell/GSC vs DGC function. It will be a very fast project, I have already discussed with the Corresponding author at Florida state university, Dr. Tang about collaborations

<http://www.bio.fsu.edu/faculty-tang.php>

Let's talk about the possibilities,

Best, Zhe

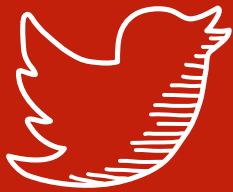
One additional element not contained in this email, but in later discussions to pursue Zika, was a report that AXL expression in GSCs served as the Zika cell surface receptor—a conclusion that has since been called into question.

As Zhu predicted, his project moved quickly.

In collaboration with laboratories at Washington University led by Michael Diamond and Milan Chheda, Zhu demonstrated that Zika was a potent and specific killer of highly resistant glioblastoma stem cells.

By manipulating the genetics of the Zika virus, even greater specificity for glioblastoma was found, based on interferon responses. After transition of the Rich laboratory to the Moores Cancer

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Center at University of California, San Diego, these studies were completed and results published in *J Exp Med* (2017 Oct)—within just a year following the outbreak.

Rapidly, other groups confirmed these findings and used additional efforts to modify the Zika virus.

Independent reports published Jan. 16 in *Cell* family journals, *Cell Reports* and *Cell Stem Cell*, originated from two groups at UC San Diego School of Medicine and Moores Cancer Center.

“Talk about chance,” Rich said to me—two labs working at the same time and

knockout cells retained the ability to be infected.

Working independently, without knowledge of each other’s efforts, the Rich laboratory—in collaboration with the laboratories of David Cheresh and Alyson Muotri at UCSD—used an extensive trial-and-error, surface integrin-antibody screen, finding that Zika killed glioblastoma stem cells to a far greater degree than normal human brain cells.

Since normal neuro stem cells also express integrin $\alpha_v\beta_5$, a therapeutic index needs to be established to specifically kill GBM cells. Tariq Rana’s lab leveraged orthogonal discovery efforts to



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same place—only to become aware of the other group’s work when notified by *Cell*, which coordinated the submissions to come out the same day. The two papers were put into context by an accompanying Perspective piece.

both identify integrin $\alpha_v\beta_5$ as an essential node in the entry of Zika into brain tumor stem cells. Rana used [CRISPR gene-editing](#) technique, selectively deleting specific genes from GBM [stem cells](#) then exposed each mutant to the Zika virus.

The elusive receptor

One of the challenges in effective oncolytic viruses has been the absence of selective viral entry into tumor cells, often because the receptors or internalization pathways have not been well characterized for a virus or the relevant tumor type.

Although AXL was initially thought to facilitate Zika entry into some cell types, this was later disproved—normal AXL

The story of Zika illustrates that viruses may be cancer’s enemy—and, to us, a valuable friend.

Rather than relying on a small number of viruses as possible therapies in a diverse set of cancers, the evolutionary drive of viruses to adapt to specific niches and cell types may offer improved therapeutic modalities to selectively target resistant tumor populations: conceptually, precision viral oncology.



GUEST EDITORIAL

What cancer immunologists are doing about COVID-19



By Rachel Humphrey, MD

Head of R&D, TIO Bioventures Discovery Engine;

Chief medical officer, Treadwell Therapeutics;

Lead singer of The Checkpoints, the house band of the Society for Immunotherapy of Cancer

It's hard to fathom the number of scientific discoveries that are exploding from the COVID-19 disaster. Though there may be tumbleweeds on every street around the globe and impotent silence in the shuttered stores of every town, the scientists at the frontline of this epidemic are busier and more energized than they've been in a long time.

The tragedy and confusion of our current reality will linger for a very long time to come, but the history of medicine is likely to look back on these months with humbled reverence and gratitude.

The strategies anyone might use to study and combat the virus are diverse, and they depend on the context and focus of a given scientist's work. Physicians who are supervising the care

of hospitalized patients have first-hand access to the natural history of the disease.

Bench scientists with access to clinical samples are uniquely suited to dissect the biological underpinnings of the clinical picture. In collaboration with an extremely responsive and supportive global regulatory community, a broad array of clinical and bench-based scientists is generating a whirlwind of hypotheses—and potential therapies are flying off the shelf. Clinical studies are starting in record time, and great ideas are speeding from white board to publication in weeks. These are the worst of times, but they are also the best of times.

To read the pulse from the front lines, I connected with a ready-made commu-

nity of world-class physicians and scientists who assembled in 2007 because of their mutual love of immunology and also because of their mutual love, of all things, music.

The group, a blues-rock band called The Checkpoints, is composed of global leaders who are leveraging their deep knowledge of the immune system to assist in the battle against COVID-19. They include multiple heads of cancer or immunotherapy departments in major American institutions, former and current presidents of the Society for Immunotherapy of Cancer (SITC), and a Nobel Prize-winning scientist (*The Cancer Letter*, [Oct. 5, 2018](#)).

What do we know today? What are these folks seeing in their COVID-19-infected patients and in their own per-

sonal scientific explorations? What are the ongoing hypotheses that drive the emerging clinical studies, and what can we say about the rapid evolution of medicine, in light of their ongoing work?

To get some answers, I reached out to members of the band and conducted structured interviews around these questions. While the content of their responses overlapped considerably, I was surprised to find that each of them came from meaningfully different angles and that their integrated story was richer than I'd found from any one member of the group. Relevant references for further reading are provided at the bottom.

Here's what I learned:

By way of introduction

As we've been hearing routinely throughout the past weeks, up to 25% of COVID-19-infected people don't experience symptoms at all and may never know that they've been infected. For everyone else, key symptoms center around the lungs, where patients' experiences could range from a benign and short-lived dry cough to deadly diffuse lung failure requiring artificial ventilation in the ICU.

What has been emerging in the last few weeks, though, is that the constellation of meaningful symptoms isn't confined to the lung. Some patients experience GI symptoms (e.g. severe diarrhea) and/or a loss of their sense of smell as the primary symptom.

Kidney injury, bone marrow reduction, and severe heart damage are also seen. A rare disorder previously associated with other viral infections and certain T cell-based immunotherapies, secondary hemophagocytic lympho-histiocytosis (sHLH), was identified in some COVID-19 subjects within the past few weeks, and the observations of phy-

sicians in the UK was published in the *Lancet* last Saturday.

Cancer doctors who have been studying the immune system for the last two decades recognize the symptoms of COVID-19 infection from their experience in oncology. To them, the constellation of toxicities in some infected patient looks like an immune response run amok.

Their thinking is that when key elements of the immune system are kick-started by the virus, an over-ambitious immune response in some patients will lead to life-threatening fulminant multi-organ failure. If this explosive blast of immunity occurs early enough in the infection, they reason, the patient may die before the virus has the chance to be fully cleared from the body.

The scientific tools we need to dissect the myriad of open questions are available in ways that the victims of the 1918 Spanish flu epidemic couldn't leverage 100 years ago. These tools include an intimate knowledge of the immune system, derived from years of study in the context of HIV infection, autoimmune diseases and cancer.

Additionally, large networks of multinational collaborations that were initiated in recent decades increased in size and number dramatically in the last few weeks. "Basket clinical studies" that enable physicians to test lots of potential therapies in a single clinical study are now opening in record times at a scale and global reach never seen before. Bioinformatics technologies to help design vaccines has also entered the scene within the past few decades.

What we know

Let's start with what we know today, and by "today" I mean observations made as recently as yesterday.

The short answer is that no one knows anything with certainty, and for that reason we must interpret the following with caution. We need to recognize that the definitive answers are still weeks, possibly months, away. Solid and scholarly hypotheses abound. They include the observations that symptoms in seriously ill COVID-19 patients resemble familiar symptoms in the settings of other viral infections and cancer.

1. "Cytokines"—helpful or hurtful?

Many clinicians are observing high serum levels of key cytokines, like IL-6 and IL-1, in the sickest patients with COVID-19. Cytokine storm is a familiar event to oncologists, seen in patients with cancer who receive CAR T immunotherapy. In this setting, the powerful anti-cancer effect of CAR Ts puts the system into overdrive, increasing expression of cytokines and creating clinical symptoms that look very much like those in critically ill COVID-19 patients. The running hypothesis, then, is that cytokine release, usually a necessary element of the normal response to viral infection, becomes unacceptably high in some patients for reasons that are poorly understood. The high levels of cytokines overwhelm normal body systems, causing injury, particularly in the lung.

Open questions here include: if cytokines are a necessary feature of the anti-viral immune responses, what are the consequences of inhibiting them in some patients? How can we distinguish those patients that must have inhibition of cytokines from those that might be harmed by it, and if we end up concluding that cytokines must be blocked, is inhibiting one cytokine enough? Do we need to inhibit in a combination of more than one? If so, which ones?

2. Cellular immunity—helpful or hurtful? The response of activated T cells to the virus is traditionally thought to be a key component of

the immune response to the virus. However, enhancing T cell immunity with T cell checkpoint blockers (e.g. CTLA-4 or PD-1 pathway inhibitors) in cancer patients can also cause life-threatening inflammation in the lungs (pneumonitis),

while the pneumonitis from COVID-19 apparently does not.

Still, caution is appropriate. The National Comprehensive Cancer Network will be releasing guidelines shortly on the treatment of cancer patients with

tem may be useful? Or is such treatment always likely to exacerbate the life-threatening symptoms? In chronic viral infections, T cell stimulators can be helpful, but what about in acute infections? Will they cause harm? What are the other predominating cells that play a role in COVID-19, and what are the implications for treatment options?



In collaboration with an extremely responsive and supportive global regulatory community, a broad array of clinical and bench-based scientists is generating a whirlwind of hypotheses—and potential therapies are flying off the shelf.



the same type of pneumonitis that is seen in COVID-19 patients. Could it be that the pneumonitis in the two clinical settings are related due to an over-active cellular immunity? Could it be that direct lung damage by the virus at the point of entry in the respiratory track increases the sensitivity of that tissue to the adverse effects of T cell stimulation, and are there already bacteria in the lung microbiome in some patients that predispose them to damage by an active anti-viral T cell response? These are questions that need answers.

Consequently, there's lots of ongoing discussion about whether it's appropriate or even safe to apply checkpoint blockade to cancer patients who are in the midst of an active, even mild, COVID-19 infection. However, there's evidence that the types of lung damage in the cancer vs. infection setting may be different, and the caution that might lead physicians to stop checkpoint blockade in cancer patients may be misplaced. Pneumonitis from checkpoint blockers respond to anti-TNF,

checkpoint blockers during the period of COVID-19 infection.

Some scientists think that T cells aren't the culprit in lung damage during COVID-19 infection. Stimulation of other cells in the lung microenvironment, like macrophages, may make the difference. If confirmed, this line of reasoning could lead to other forms of therapy during COVID-19 viral infection. Interestingly, anti-malaria drugs like chloroquine and hydroxychloroquine inhibit production of pro-inflammatory cytokines by antigen presenting cells and macrophages, and this explains in part why clinicians have tested their use in infected patients. However, anti-malarial drugs don't have target specificity and may be inhibiting desirable biological functions that patients need to fight the virus. Antibodies, which more precisely target specific cytokines of interest may be better suited to treat patients.

Open questions here include: Is it ever appropriate to amplify the T cell response as a means of clearing COVID-19 faster, perhaps early in the infection when such a boost to the immune sys-

3. The timing of the various immune responses may matter. In the normal response to an infection like COVID-19, all elements of the immune system may be important. Antibodies, a first pillar in the immune system, can directly clear virus, and/or mark virally infected cells for destruction. T cell stimulation, a second pillar, causes a direct attack on virally infected cells, as it does for cancer cells, and cytokines, the third pillar, play a role as non-specific overarching stimulators of immune function. The timing, relative importance and/or relative magnitude of these independent and interdependent elements of the immune system likely impacts the course of COVID-19 infection. Each arm of the immune system causes a different constellation of symptoms, depending on the magnitude of the response. Each arm is activated at different times in the immune response and the choreography between them is likely an important factor in patient outcome.

Open questions here include: can we use therapeutic intervention to impact the timing and magnitude of multiple arms of the immune system, and, again, can we better select patients who need one type of immune support over another?

4. Key differences between people may impact how they respond to the virus. The conditions within each person that govern how they might respond to the COVID-19

virus clearly differ between people. Otherwise, we wouldn't be seeing such a diverse array of outcomes. But what are these differences? Candidates include genotypic differences (e.g. HLA type), phenotypic differences (e.g. age of condition of the immune system) or environmental elements (e.g. the patient's lung microbiome, the size of mechanism of viral inoculum, co-morbidities like cancer or other infirmities).

An open question that covers all the hypotheses: as we drive a better understanding of *which* drugs to give these patients and *when* to give them, one big open question is at *what dose* and *for how long*.

In pursuit of the answers

In response to this massive list of incoming observations, hypotheses and uncertainties, physicians and scientists around the world are rapidly creating resources to answer these questions. Taskforces are forming. Dropboxes filled with papers are being populated and shared. Clinical protocols are being disseminated and conducted widely. Cytokine panels are being added to research—and lots of information is already out there.

At the University of Chicago, where Thomas Gajewski, AbbVie Foundation Professor of Cancer Immunotherapy, is spearheading the bedside to bench to bedside work, there is a systematic effort to understand who benefits from the candidate therapies and who doesn't. Bio-banked serum from cancer patients who experienced pneumonitis from checkpoint blockade is being compared to newly bio-banked serum from COVID-19 patients, with some of those patients receiving anti-viral agents, cytokine blockers, or hydroxychloroquine. In this way, the two fields are learning from each other.

Resident microbes in the airways are being evaluated from the diagnostic nasal swabs. That material is being sequenced to see if specific microbiotal patterns predispose some patients to worse outcomes than others. Germline polymorphisms that are known to be linked to susceptibility to other viruses are also being evaluated in the context of the course of COVID infection.

The magnitude of the T cell and Ab response is being analyzed with respect to viral clearance as well as immune pathology. This work will be very important in defining opportunities to develop treatments in real time—building on the learnings from oncology to serve the current state of the pandemic.

At the University of Pittsburgh Medical Center, a broad catchment of patients across a community cancer network may enable bio-clinical sample collection from a wide range of patients (healthy and sick). There, Jason Luke, associate professor of medicine in the Division of Hematology/Oncology and the director of the Cancer Immunotherapeutics Center within the UPMC Hillman Cancer Immunology and Immunotherapy Program, and his colleagues plan to prospectively follow the natural history of the illness and determine which patient characteristics, from among the full spectrum of those listed above, are associated with various forms of viral response.

Routine screening of up to 1,000 patients to see who becomes sick over weeks or months will make a valuable contribution to the treatment of this virus over time. Early serological evidence of metabolites of cytokines, for example, may predict who will get sick. Following the magnitude and pattern of changes over time could help time therapeutic interventions. Hence, while others are looking to find therapies now, Dr. Luke's teams are thinking ahead to better understand the natural history

of the disease for people with all types of clinical responses.

At UCLA, John Timmerman, associate professor of medicine at the UCLA Lymphoma Program, is encouraging local efforts for transfer of convalescent serum from recovered patients into sick patients, a strategy that is underway around the world. This approach, successfully developed by the early pioneers in immunology in the 1918 Spanish flu pandemic, has also been used to treat outbreaks of polio, measles, and mumps. Hence, under Dr. Timmerman's care the principles of sero-therapy laid out by Pasteur, Koch, and Erlich are being explored in collaboration with doctors at The Johns Hopkins hospital.

At the Parker Institute for Cancer Immunotherapy, Lisa Butterfield, vice president of research and development, and the teams in clinical development and informatics are working to widely distribute informatics technologies and standard operating procedures for immune profiling) and strengthening and unifying procedures so scientists and clinicians can work from the same toolbox.

At Washington University in St. Louis, Dirk Spitzer, assistant professor of surgery, and his team is in the process of developing a therapy that is based on blocking the virus from entering the host cells using soluble ACE2 receptors. This approach is considered relatively straight forward, is universally applicable, and does not require generation of monoclonal antibodies.

Once the biologics have been validated in tissue culture, animal work in ferrets, a species that has been recently reported to support replication of SARS-CoV-2 leading to COVID-19 like symptoms, will be conducted. If studies in ferrets show reduction in symptom severity upon administration of soluble ACE2 biologics, an expedited transition into the clinic is envisioned.

Among the myriad of agents in testing around the world, there are many strategies. (1) anti-viral drugs as an early intervention, (2) blockers of immune overactivity to prevent cytokine storm, and (3) passive immunity (antibody transfer) for those whose own immune system is failing to clear the virus. Arguably the biggest holy grail, vaccination for prophylaxis, is a clear focus of the work of scores of teams around the world.

As of today, nothing has been definitively proven to be effective, but we'll get there. I've no doubt. The sheer magnitude and speed of the effort is impressive. The remarkable collaboration between doctors, scientists, regulators and patients cannot be underestimated.

Pulling it all together

Pulling it all together, it's easy to see that lots of organizations are racing to the cure for this unprecedented and tragic global pandemic. In their work, they are building from learnings across therapeutic areas to find and define a new "mechanism-based" backbone of medicine. On the shoulders of giants, these talented men and women use their understanding of the immune system to guide effective therapies for the deadly COVID-19 infection.

"The remarkable thing," John Timmerman says, "is that our understanding of the immune system was relatively primitive until the early 1980's, when monoclonal antibody technology was introduced. This allowed us for the first time to characterize immune cells based on surface markers (CD antigen system). When the HIV epidemic arrived in the early 80's, we began to understand the immune system and the effects that this devastating HIV virus had upon it. Billions of dollars flooded into immunology research around the world and led to a deepening of our understanding of immune regulation.

"A decade later, this knowledge was ready to be applied to the field of cancer immunotherapy. Therefore, the HIV epidemic, as catastrophic as it was, helped to catalyze the modern science of immunology and, interestingly, has now led us to a high level of understanding that we need to tackle the current COVID-19 pandemic.

"Interleukin 2 (IL-2), an important cytokine, was first identified by Robert Gallo in the early 1980's at the NIH in the context of the AIDS epidemic. The IL-2 was then used to cultivate CD4 cells and to grow HIV in the laboratory. Later, recombinant IL-2 was used by Steve Rosenberg (Chief of the NCI Surgery Branch) in high doses to treat cancer, leading to some of the earliest successes in anti-cancer use of the immunotherapy. Here we come full circle from AIDS to cancer and to COVID-19, as oncologists bring the knowledge we have in cancer immunotherapy back to our colleagues studying severe viral infections."

We can't forget, though, that this long list of anecdotes and great ideas is swirling in a sea of a global pandemic—with thousands of patients sick or dying, health care workers risking their lives in the service of the greater good, lab workers redeployed to support patient care, and a world full of people holding their breath in the hope that their loved ones stay well. To those who are truly at the front line of care we offer sincerest thanks.

Together we'll get through it—with all hands on deck.

For further reading:

- Yufant Shi et al. COVID-19 infection: the perspectives on immune responses. *Cell Death & Differentiation*. 10 March 2020 (<https://doi.org/10.1038/s41418-020-0530-3>)

- Mehta P et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 28 March 2020. ([https://doi.org/10.1016/S140-6736\(2\)30628-0](https://doi.org/10.1016/S140-6736(2)30628-0))
- Mukherjee S. How Does the Coronavirus Behave Inside a Patient? (<https://www.newyorker.com/magazine/2020/04/06/how-does-the-coronavirus-behave-inside-a-patient>)
- SITC Statement on anti-IL-6/IL-6R for COVID-19 (<https://www.sitcancer.org/research/covid-19-resources/il-6-editorial>)
- Conti P et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVID-19 or SARS-CoV-2): anti-inflammatory strategies. *Biol Regul Homeost Agents*. 2020 Mar 14;34(2). pii: 1. doi: 10.23812/CONTI-E. [Epub ahead of print]
- <https://jamanetwork.com/journals/jamaoncology/fullarticle/2763673>
- Li W, et al. Cancer Patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet* 21 March 2020. ([https://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045\(20\)30096-6.pdf](https://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(20)30096-6.pdf))

The following individuals contributed to this story: Brad Reinfeld, MD, PhD student at Vanderbilt University Thomas Gajewski, AbbVie Foundation Professor of Cancer Immunotherapy, University of Chicago Jason Luke, director of the Cancer Immunotherapeutics Center within the UPMC Hillman Cancer Immunology and Immunotherapy Program, John Timmerman, associate professor of medicine at the UCLA Lymphoma Program, Lisa Butterfield, vice president of research and development, Parker Institute for Cancer Immunotherapy, Dirk Spitzer, assistant professor of surgery, Washington University in St. Louis.

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

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CONVERSATION WITH
THE CANCER LETTER

A COVID-19 update from New York:

**“The only thing I hear at night
now is the wail of ambulances”**

“

I don't think anybody who's alive has experienced anything like this at all, unless they've possibly been in a war zone. Even then, this is a very unusual war zone.

”



Benjamin Neel, MD, PhD

Director, Laura and Isaac Perlmutter Cancer Center;

Professor, Department of Medicine, New York University Grossman School of Medicine

It's a jump that's hard to fathom:

Two weeks ago, there were 600 detected COVID-19 cases in the state of New York. At this writing, there are over 100,000 confirmed cases, a 170-fold increase that has filled hospitals and depleted medical supplies at an unprecedented scale.

"I don't think anybody who's alive has experienced anything like this at all, unless they've possibly been in a war zone. Even then, this is a very unusual war zone," said Benjamin Neel, director of the Laura and Isaac Perlmutter Cancer Center and a professor in the Department of Medicine at the New York University Grossman School of Medicine.

"Certainly, I haven't experienced anything like this," Neel said to *The Cancer Letter*. "I think it's pretty clear that this is the largest public health emergency, easily, in this century—probably the biggest since the avian flu epidemic in 1918—and maybe the largest public health emergency in the history of the country."

According to 2016 data from the American Hospital Association, 6.1% of New Yorkers are uninsured, and there are 2.66 beds per 1,000 New Yorkers.

Over half of the 100,000 cases statewide were detected in Manhattan and the four neighboring boroughs, making New York City the latest epicenter of the COVID-19 outbreak—nearly 1,600 have died at this writing. City data show that the 2,449 intensive care unit beds are nearly at capacity, even as health officials expect more patients to show up.

At the NYU Langone Health system, a surge of patients sickened by SARS-Cov-2 has filled its hospitals, forcing the reopening of Tisch Hospital—one of the older hospitals that has been partly closed.

"Our hospital is pretty close to its normal capacity in beds. The hospital has

been transformed into a largely COVID hospital," Neel said. "Also, we've used other facilities that are adjoined to our superblock to expand our capacity.

"I hear that we still have another seven to 10 to 14 days—I'm not really an expert on that estimate—but we have more time to go and more patients will be coming in. I'm confident that [the curve is] not flattening that much."

Patients with cancer, too, are showing up with evidence of COVID-19.

"We've seen patients come in for presentation with a likely abdominal neoplasm, and they have ground glass lesions on their lungs that are now sort of recognized immediately as COVID, and they're asymptomatic," Neel said.

Updated data from Italy show that about 16.5% of people who die from COVID-19 are patients with cancer, based on a sample of 909 patients. The vast majority of patients in the study sample have one or more comorbid conditions. An earlier review of the fatality

DATA FROM ITALY: MOST COMMON COMORBIDITIES OBSERVED IN COVID-19 POSITIVE DECEASED PATIENTS

Diseases	N	%
Ischemic heart disease	249	27.4
Atrial Fibrillation	209	23.0
Heart failure	149	16.4
Stroke	109	12.0
Hypertension	668	73.5
Diabetes	286	31.5
Dementia	146	16.1
COPD	166	18.3
Active cancer in the past 5 years	150	16.5
Chronic liver disease	42	4.6
Chronic renal failure	216	23.8
Number of comorbidities		
0 comorbidities	19	2.1
1 comorbidity	197	21.6
2 comorbidities	223	24.5
3 comorbidities and over	470	51.7

The most common comorbidities diagnosed before COVID-2019 infection. Data on diseases were based on chart review and was available on 909 patients dying in-hospital for whom it was possible to analyse clinic charts. Mean number of diseases was 2.7 (median 3, SD 1.6). Overall, 2.1% of the sample presented with a no comorbidities, 21.6% with a single comorbidity, 24.5% with 2, and 51.7% with 3 or more. Before hospitalization, 28% of COVID-19 positive deceased patients followed ACE-inhibitor therapy and 16% angiotensin receptor blockers-ARBs therapy. This information can be underestimated because data on drug treatment before admission were not always described in the chart.

Source: Istituto Superiore di Sanità, Servizio Sanitario Nazionale, Ministero della Salute

estimates is available [here](#) (*The Cancer Letter*, [March 20](#), 2020).

On-site physician encounters for medical oncology at NYU are down by more than 50% as the Perlmutter Cancer Center moves its operations online.

“We’ve really pretty much changed our practice paradigm. Many visits are being done remotely. Initially, they were by phone visit, but right now, largely by telemedicine,” Neel said. “We find that roughly 75% of our patients can do that. Almost everybody has access to the types of technology that you need to do it.

“We’ve instituted very increasingly stringent screening protocols for patients coming into our outpatient centers across our network, which spans Brooklyn, Queens, Manhattan, Staten Island, even, and Long Island. We’ve excluded visitors, with very few exceptions, from the cancer center.

“Everybody gets their temperature taken at the door. We have a very robust screening questionnaire. So, everything is completely changed. Clinical research is significantly impacted, obviously.”

Cancer specialists are being reassigned to inpatient services as NYU hospitals fill with COVID-19 patients.

“We currently have two heme-onc attendings on the inpatient service and serving as medicine attendings. Three of our fellows, two of them at NYU and one at Bellevue, our affiliate, have stepped up,” Neel said. “I know that similar situations are occurring at our satellite campuses at NYU-Winthrop and NYU-Brooklyn.”

In a March 21 news briefing, New York Governor Andrew Cuomo announced that 40% to 80% of the state’s population is likely to be infected by the novel coronavirus. This translates into about 7.8 million to 15.6 million New Yorkers.

“Younger people listen up: 55% of NYS #Coronavirus cases are ages 18-49,” Cuomo wrote in a March 21 tweet. “Young people aren’t invincible. You can get this and you can give it to someone older you love. You shouldn’t endanger your own health & you certainly shouldn’t endanger other people’s health. #StayAtHome”

The stay-at-home orders were, unfortunately, “a little late,” because of a delayed national response, Neel said.

“I think, obviously, we lost a month of time,” Neel said. “‘We’ being the United States—not New York City—lost at least a month of time in not being adequately prepared with having enough testing and enough materials and supplies for this current situation. So, that’s the thing that would have helped. And again, probably acting earlier to impose social distancing and things like that.

“But it’s sort of like a double whammy—if you don’t have enough testing to rapidly trace contacts and isolate them and enforce that, then you get rapid spread and that’s what happened. But again, I don’t think this is a situation that anybody in their experience, at the government level, expected either.

“It would have been better if people grasped that in advance, but once people saw what we were looking towards, people take it very seriously. Manhattan is pretty busy. I live on a busy street, but the only thing I hear at night now is the wail of ambulances.”

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

Matthew Ong: The eyes of the world are on New York City at the moment. Have you experienced anything like this in your career as a physician?

Benjamin Neel: Well, I don’t think anybody who’s alive has experienced anything like this at all, unless they’ve possibly been in a war zone. Even then, this is a very unusual war zone. Certainly, I haven’t experienced anything like this.

I think it’s pretty clear that this is the largest public health emergency, easily, in this century—probably the biggest since the avian flu epidemic in 1918—and maybe the largest public health emergency in the history of the country. So, I think that none of us have experienced anything like this.

Can you describe what you’re seeing on a daily basis? What changes have been made at your health system and in your cancer center?

BN: I don’t see patients, so I actually haven’t been at the cancer center since two weeks ago. I actually was home, because I thought I had a mild sore throat and some congestion, and I wanted to make sure I wasn’t getting it, so I stayed home for seven days and right before the end of the seventh day, I, being not used to being at home during the day, so I was walking really fast, like I walk outside, and I definitely broke my toe, and maybe a bone in my foot.

So, I’m just working completely from home for pretty much 18-hour days. It’s amazing how much you can get done remotely. I think that’s going to be one of the changes that the health system realizes as a consequence of this emergency.

Well, first of all, I should say that the physicians and nurses and staff at NYU Langone and the leadership have just been incredibly impressive in terms of their response to this crisis. The hospital has been transformed into a largely COVID hospital, and the hospital man-

agement has done a really remarkable job of adapting to really very dramatically changing conditions on an almost minute-to-minute basis.

My colleagues, particularly those on front line, patient-facing physicians that are seeing this—the emergency room docs, the respiratory docs, the intensivists—they’ve really done amazing work. I think that’s probably true across the whole city and the metro area.

At the cancer center, I think that our physicians also have really stepped up and some of them have actually been redeployed to inpatient services. We currently have two heme-onc attendings on the inpatient service and serving as medicine attendings. Three of our fellows, two of them at NYU and one at Bellevue, our affiliate, have stepped up. I know that similar situations are occurring at our satellite campuses at NYU-Winthrop and NYU-Brooklyn.

But then, in the cancer center itself, we’ve really pretty much changed our practice paradigm. Many visits are being done remotely. Initially, they were by phone visit, but right now, largely by telemedicine. We find that roughly 75% of our patients can do that. Almost everybody has access to the types of technology that you need to do it.

Almost all new visits are being done by telemedicine, with patients evaluated as for how emergent the visit would be, and arrange for labs and scans and other tests to be done first. Then, on the day that they come in, they would see their physician before they start therapy. We’ve also decreased routine revisits.

People are coming in for regular therapy. Our infusion volume is down somewhat, but it’s not in any way down the way our “in person” physician-encounter visits are down. Patients are basically having usually telemedicine visits the night before to make sure everything’s okay, and then, they come to the cancer cen-

ter and get their infusion. Or sometimes, it’ll be coordinated so that they come to the cancer center and are seen by their physician before they get their therapy.

We’ve instituted very increasingly stringent screening protocols for patients coming into our outpatient centers across our network, which spans Brooklyn, Queens, Manhattan, Staten Island, even, and Long Island. We’ve excluded visitors, with very few exceptions, from the cancer center.

Everybody gets their temperature taken at the door. We have a very robust screening questionnaire. So, everything is completely changed. Clinical research is significantly impacted, obviously. Several of our providers, nurses and staff have contracted the disease. Fortunately, everyone is doing well. Many of them are back at work.

At this rate, how many New Yorkers are expected to contract the coronavirus, based on projections so far?

BN: There are various assessments about what fraction of the population in New York is going to get this virus. It’s pretty high. The numbers have a large variance. I think the governor [Andrew Cuomo] even said up to 80% at one point. I think there’s going to be variation in those numbers. Clearly, a lot of people.

Do those estimates account for undetected cases, etc.?

BN: I think, actually, that number probably does. I don’t think he’s saying that 80% would be symptomatic, because if 80% were symptomatic, 100% would be infected. I think he’s actually taking the higher number. I think you’ve raised

an interesting point though, is that when the public listens to these various estimates, they may not be hearing the same estimate, or the estimate may not be based on the same facts.

There is a significant number of asymptomatic patients, and, of course, that’s been a real challenge. Probably the most important factor in driving this pandemic to where it is, is the asymptomatic transmission.

I don’t even remember—I guess it’s been maybe three weeks since the last time things even began to approach normal around here—our planning began in late January, early February. But I don’t think that anybody could have anticipated the scale and scope of the problem.

I am in no way a water carrier for administration above me—I don’t always agree with every decision they make—but that notwithstanding, I think they’ve done a really good job. I think they’ve inspired a lot of confidence for everybody who’s working here. So, we’re just trying to do our part at the cancer center.

Have beds that are designated for the cancer center been converted for inpatient emergency purposes?

BN: We don’t have a freestanding cancer center with separate beds, so, that’s not an issue. In Manhattan, we have a large outpatient cancer center on 34th Street and the satellite overflow cancer center on 38th Street. Cancer doesn’t really stop, so we still have a very large number of patients who are getting treated, and we continue to see patients. There’s no plan to close any of our cancer infusion centers or outpatient centers. They’re all open. That goes for all of our sites across the network. Obviously, they’ve all seen a drop in volume.

Much of that is intentional on our part, because we want to make sure that our patients and our staff are safe, to the extent possible. Particularly our patient population, which is highly enriched for immunosuppressed or frail, patients with comorbidities—the kind that are exactly the ones who do extremely poorly with this disease—but our cancer practices are open everywhere. We do have an inpatient floor for bone marrow transplant and for the heme-onc service, and the number of inpatients is markedly less than it normally would be. All elective bone marrow transplants or semi-elective bone marrow transplants, of course, have been suspended.

Note, and again, this is, in many ways, largely motivated by the fact that we don't want to expose our patients to risk in traveling here and possibly encountering other COVID patients in the immediate aftermath, but also obviously for resource preservation.

We still have a small inpatient service. It's smaller than it normally would be, and we always do our best to keep people out of the hospital. I used to say when I was an intern and a resident that the hospital is a horrible place to be, unless you need to be there. I think that's still true. We try to keep our patients out of the hospital normally, but we're doing everything we possibly can to make sure that our patients get the best care outside the hospital, and have the least transit to any of our centers as possible.

Again, I literally have not left my apartment for two weeks, except to go downstairs one day to pick up a package. There was a lot of grumbling among city residents in the first couple of days, but I think, in fairness, most New Yorkers have taken this quite seriously since we shut down.

Unfortunately, it was a little late. It would have been better if people grasped that in advance, but once people saw what we were looking towards, people take it very

seriously. Manhattan is pretty busy. I live on a busy street, but the only thing I hear at night now is the wail of ambulances.

What do you think happened here? Yes, New York City is the most populous and the most densely populated city in the U.S., but what strategies would have helped slow the spread in the U.S. if put in place earlier? What are your thoughts?

BN: Well, I think, obviously, we lost a month of time. “We” being the United States—not New York City—lost at least a month of time in not being adequately prepared with having enough testing and enough materials and supplies for this current situation. So, that's the thing that would have helped. And again, probably acting earlier to impose social distancing and things like that.

But it's sort of like a double whammy—if you don't have enough testing to rapidly trace contacts and isolate them and enforce that, then you get rapid spread and that's what happened. But again, I don't think this is a situation that anybody in their experience, at the government level, expected either.

We've all seen many stories about hospitals in New York running out of beds and health care workers running out of supplies and PPE, and dead bodies being stored in refrigerated trucks—a scene eerily similar to what we've seen in Wuhan and Lombardy. Have you heard from your health system on these issues, and are you facing any of these challenges as well?

BN: Well, our hospital is pretty close to its normal capacity in beds. First of all, our main hospital is new. It's only been open for a year and a half. Again, I don't mean to make this sound like an advertisement, but I think that the way our management designed the hospital, actually, put us in a much easier position, because every room was designed to be converted to a negative pressure room. So, that helped a lot in terms of converting things to ICUs, and things like that, very quickly. So, that helped.

We also had our old hospital, Tisch, that was partly closed, and there were plans being made for how it was going to be renovated and used to expand our capacity in the future. Tisch, which until two years ago, was our main hospital, has now been reopened and redeployed for taking care of excess patients.

Also, we've used other facilities that are adjoined to our superblock to expand our capacity. So, we are still taking patients and giving them outstanding care.

But I hear that we still have another seven to 10 to 14 days, I'm not really an expert on that estimate, but we have more time to go and more patients will be coming in. I'm not directly involved in those discussions. There are lots of other contingencies being looked at to try to deal with these patients. I don't speak for NYU Langone overall, but I know NYU Langone's philosophy, and we put patients first. We've always been a patient-centered institution, and we continue to be patient-centered through this pandemic.

What are your staff hearing from your cancer patients, existing or new? And are they seeing cases among your patients who have cancer?

BN: We have had a few cases of cancer patients with COVID disease. I know from talking to my colleagues that they've had some patients who've had COVID disease. What we often see is unanticipated COVID disease. There was a case the other day that was a patient in the surgical service who was asymptomatic, but had telltale signs on their chest imaging.

I will say one thing: there hasn't been a lot good to come out of this epidemic, but one of the things that's helped our place is it's actually really motivated more use of multidisciplinary tumor boards, and things like that, to make decisions about care.

So, if you don't have, basically, unlimited surgical capacity anymore, because you need to conserve resources and space for COVID patients, a lot of issues that would have been decided without multidisciplinary input, now are getting decided in multidisciplinary tumor boards, which is great for us. It's been something that the cancer center has been trying to promote for a long time.

But we've seen patients come in for presentation with a likely abdominal neoplasm, and they have ground glass lesions on their lungs that are now sort of recognized immediately as COVID, and they're asymptomatic. Or they have a story that they had a cough two weeks ago and now they're fine. So, yeah, we're seeing that happen sometimes.

We're seeing people come to the door with a fever that ordinarily we would just work up, but they're usually viewed as presumptive COVID and sent home if they're stable, or to the emergency room if they're not. So, yes, this does not spare cancer patients, doesn't spare cancer doctors, doesn't spare cancer nurses. It doesn't spare staff at cancer centers.

You spoke briefly about telehealth earlier—has NYU Langone had a robust program for a while now? And have you overcome so many of the other challenges that I've heard about from other health systems who are developing telehealth programs?

BN: It was just relatively recently that we've been moving towards having a telemedicine capacity, but necessity is the mother of invention. When it became clear, about a month or six weeks ago, or maybe even longer, that this was going to be a problem in terms of potential strain on our outpatient facilities, management really was able to move quickly and get it established across the network, especially for cancer services.

As I said, there is very heavy utilization of telemedicine now by our medical oncologists. That's been able to be improved over what was being done in the initial weeks, which was just phone visits where possible. On-site physician encounters for medical oncology are down by more than 50%, and they've largely been supplanted by telemedicine visits with a few phone visits in between.

Right, you were talking about early preparation for the pandemic in January.

BN: I hate to talk about advantage in a situation like this where no one has any "advantage," but we had the disadvantage of suffering from Sandy, and I wasn't here then, but I know from my colleagues the stories of how that happened.

I think that this administration at NYU was the same people who were able to bring us through the Sandy experience. They're very experienced in crisis management, so I think they got a very early start. The hospital executives got a very early start in really trying to think through all aspects of the upcoming problem.

Those planning sessions began in late January, for sure. On the research side even, we were getting communications about having contingency plans. I have oversight of seven floors in the research building too, and I have sitting on my computer a contingency plan for every lab.

I have everybody's contact information.

There are hierarchies of notification inside every lab. All this stuff was planned considerably before the laboratory-based research was curtailed so much.

How are you handling basic research as well as clinical trials?

BN: All the laboratories in the cancer center that are in my space are supposed to be reporting their temperatures for every individual in their lab, morning and night. The other thing that's been remarkable is to find out how many people don't have a thermometer.

Thermometer availability at the pharmacies was one of the first casualties of COVID. You can't get a thermometer anywhere in New York, I don't think. But they report in, every day, because I want to keep track of our cancer center researchers.

So far, I think we've only had one rotation student in one lab who has COVID. He's not a clinician. Some of our clinicians who have labs, they got COVID, but

they didn't get it in the research cancer center. They got it in the outside world.

It might be too early, but are there signs that the rate of detected new cases in New York is slowly flattening as a result of containment measures, i.e. social distancing policies? What are you seeing in the reports coming out so far?

BN: Well, it's a little early to tell. We've had a couple of false glimmers of hope. In the first couple of days last week, the cases were doubling every three days. Then there was a report that they were doubling every 4.7 days and there was a little glimmer of hope.

I must say I didn't look at yesterday's statistics, because we have a meeting every day. We don't really have a formal command center at the cancer center, but we have a formal clinical/research-integrated-across-the-network executive session every day from 5 p.m. on, and I think the world record for ending was 8:45 p.m. I can't thank these people enough for what they are doing for the center and for patients.

The first week when we had this, we had them on the weekend, too.

We met every day from 5 p.m. to 7 or 7:30 p.m. Then, after that, we felt it's really important to try to maintain as much communication and transparency with the physicians and staff as possible.

And, I must note, in these meetings how great all the network partners have been, as well as the clinical leaders in medical oncology, radiation oncology and surgical oncology.

My wife doesn't make dinner anymore, because it was getting burned all the

time. So, I go and I write these newsletters every night, one for the physicians and APPs, and one for the staff. That usually doesn't get done until 10, 10:30 p.m. And then, usually, I have some other work to do. And I'm up again at 5.

I think I did hear that there was some indication that there might be some flattening. But others are saying peak COVID is seven to 10 days away. So, I haven't had a chance to critically evaluate that, but I'm confident that it's not flattening that much.

It's early days, again, but if there's anything that we can learn, what have we learned so far from our handling of this pandemic?

BN: That's a political question that I don't want to address in my capacity. I have very strong political views about the central government's response to this, but I will not be able to give you those in the context of my position.

Got it. Did we miss anything?

BN: This I will say, as sort of a semi-political comment. I think the healthcare industry, the pharmaceutical industry, everybody who's involved in health care in the United States, gets a lot of criticism. Increasing amounts of criticism. But I don't hear a lot of people in the public criticizing doctors, nurses, and front-line personnel.

Actually, everybody's hoping that the pharmaceutical and biotech industry can get a vaccine, or get some good drugs for this disease. So, I think that's been a lesson that a lot of people haven't commented on too much. But I've certainly noticed it.

Every day at 7 p.m.—well, I don't often hear it, because there's not as many apartment buildings around here, or maybe it's just because most of the people up here have left or they're doctors and are not home yet—but every day at 7 p.m., when we're on this call, somebody's got their window open, and we hear people come out and shout for the doctors and first responders. There's a cheer every day. Every night at 7 p.m., they do that.

I see the Empire State Building out my bedroom window, and it was lit up for medical responders and first responders. I think that the response of the people taking care of these patients has been truly heroic, and that's a word that I don't use a lot, because I think it's grossly overused. But in this case, it's totally true.

Those intensivists and those emergency ward docs, they're overwhelmed. We have multiple intensive care units now that weren't there three weeks ago, and they're all being staffed. I would say, almost without exception, at our center, physicians, nurses, and other advanced practice personnel have realized that that's why we're in this business, and we have to do whatever it takes.

On the cancer center side, I think that it's very important that we do whatever we can to maintain the cancer services while this is going on, because cancer doesn't stop just because there's a virus raging through the community. So, I think we're doing a good job of doing that. I think our patients are getting treated well.

So far, I think that nobody's going to have an adverse outcome for their cancer from this pandemic. That's our main goal. And that's why we're working to constantly adapt, because viruses generally take advantage of their hosts by adapting, and we need to do the same.

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

A



CONVERSATION WITH
THE CANCER LETTER

As Italy's COVID-19 incidence curve flattens, Curigliano sees lessons for the U.S.

“

In my country, we have a nationalized health system, and we reduced everything. We have clear numbers. We know how many people are dying, because we are transparent.

”



Giuseppe Curigliano, MD, PhD

Associate professor of medical oncology, University of Milano;

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

Social isolation and containment have begun to flatten the curve of COVID-19 cases in Italy, Giuseppe Curigliano said to *The Cancer Letter*.

If the country stays under lockdown until at least the second weekend of April, the curve will go down, said 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.

"I am very optimistic now, because, you see, it's really a flat curve here. The number of new cases is decreasing, and it's quite clear we're going to achieve something better," Curigliano said.

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](#)).
- Curigliano: Italy's COVID-19 cases keep rising; maybe next week the curve will flatten (*The Cancer Letter*, [March 27](#)).

Italy's Prime Minister Giuseppe Conte mandated a complete lockdown of the country in early March. The U.S. federal government has yet to order a nationwide lockdown. Rather, states are responding to the threat as they see fit.

While New York has the highest number of cases of COVID-19 today, Florida and Texas are among the states that are expected to see a rapid spike in newly detected cases in the near future.

Does Curigliano see the curve flattening in the United States at the same rate as Italy?

"You are rising. On the horizon, I don't see this curve flattening," Curigliano said. "You are 50 states—any state with a specific local governor will decide what to do and what not to do. I believe you will have 50 curves that will be completely different in the country—at different times."

The solution is social isolation and total lockdown, Curigliano said.

"There is a solution to the spread, and this has been demonstrated in China. It is going to be demonstrated in Italy. The only solutions are not drugs or clinical studies. The only solutions are social isolation and containment—containment in the areas where you have a lot of people infected," Curigliano said.

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

Alex will continue to check in.

Alex Carolan: How is your family?

Giuseppe Curigliano: My family and my wife is fine, also. We survived.

That's great. How are your patients doing? Do you have more patients with COVID-19 than when we spoke last week?

GC: We have more patients. This morning, we received another patient, who is a young patient with early breast cancer that is triple negative. She was receiving adjuvant chemotherapy for early breast cancer. She was hospitalized for pneumonitis.

Has she tested positive for coronavirus?

GC: Yes. She has tested positive.

How many patients total now does your hospital have?

GC: My hospital actually has something like 10 patients positive.

I think last week at this time it was eight; right?

GC: Yes. We have two more patients.

Are these patients who are entering the hospital with no symptoms, and then they show symptoms after?

GC: Yes, usually when they start treatment they have no symptoms of COVID-19 infection. Just after starting chemotherapy, they developed COVID-19.

Right. So, after chemotherapy, basically, they show symptoms of COVID-19, and then you treat them for it?

GC: Yes, correct.

A couple weeks ago you mentioned you had a patient with lung cancer who had pneumonitis and symptoms of COVID. How are they doing?

GC: Yes. He recovered. He was dismissed by the hospital on Monday morning. He survived it. Now, we should wait at least one week, and then he will do the test again. If negative, he will come back to the hospital to receive treatment again.

Have you seen any patients who have developed COVID-19 after recovering from the disease?

GC: No, until now, no. I know that some patients have been described, but not in my experience.

That's good to hear. I'd like to start where we usually do—what the numbers look like in Italy. How many cases of COVID-19 are there?

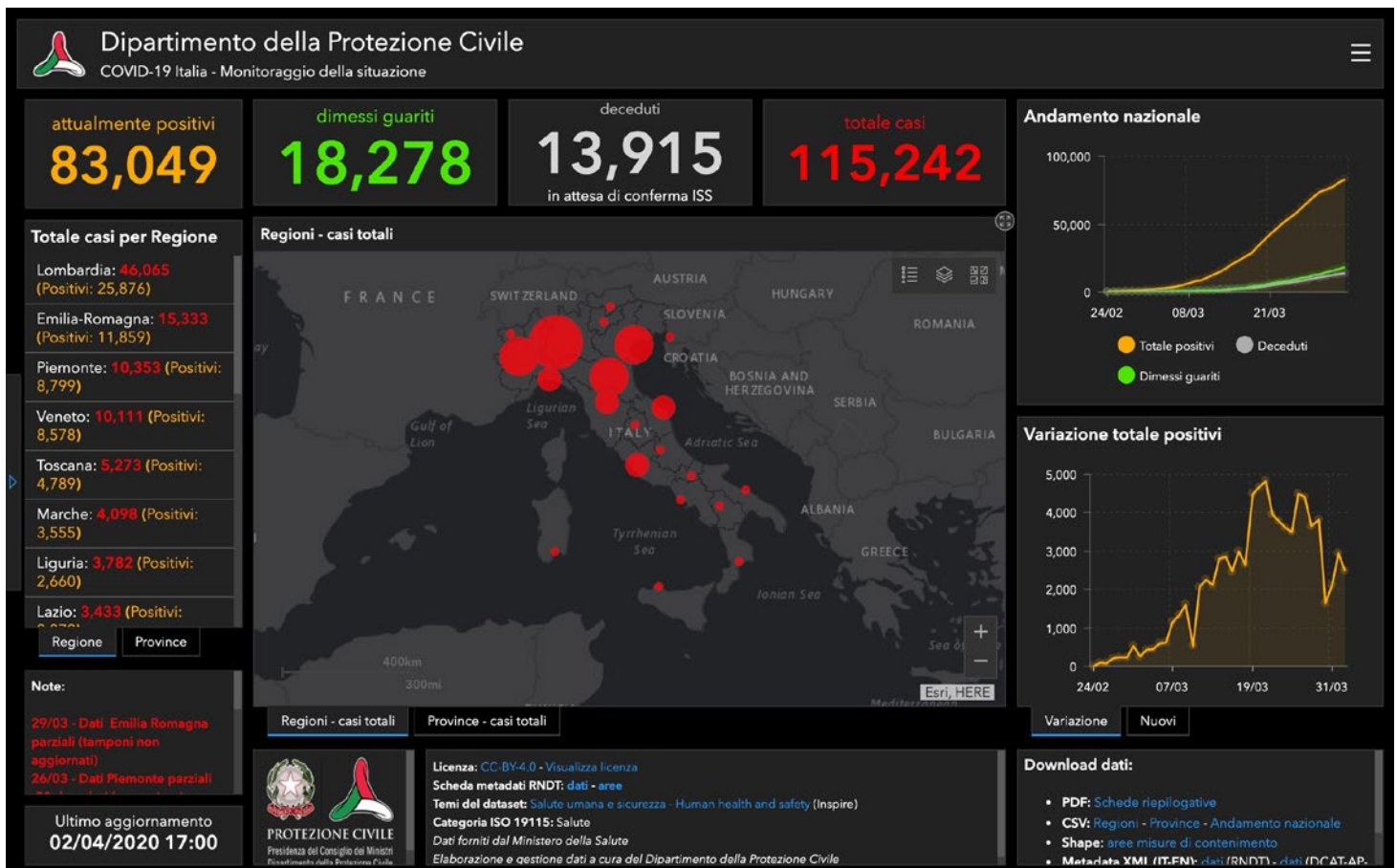
GC: We have 115,242 patients. It's a huge number—and the patients who died are 13,915. It's a really huge number. I just heard from some friends from Spain, and they arrived at 10,348 deaths in three weeks. So, it's really dramatic.

Are the numbers still going up the same amount?

GC: No, no—actually, we are going to reach a plateau. If you look here, we are in the plateau. We are going to flatten the curve. Now it's more clear.

When do you expect to see the number of cases go down?

GC: So, if we maintain the lockdown until Easter, I am quite sure that for middle April it will go down. I am very optimistic



Source: Italian Department of Civil Protection (April 2, 5:00 p.m.)

now, because, you see, it's really a flat curve here. The number of new cases is decreasing, and it's quite clear we're going to achieve something better.

You previously mentioned that cancer patients who test positive for COVID-19 have about a 20% mortality rate. Is this still the case?

GC: We had an update—actually, the number for cancer patients is 16.5%, so, less than 20%. Most of the cases are non-small cell lung cancer, head and neck cancer, and patients who are smokers and with hypertension.

Where are these numbers from?

GC: The Istituto Superiore di Sanità, the National Institute of Health [in Italy].

In terms of treatment for COVID-19, *The Cancer Letter* published an article on a class of drugs used for immunotherapy—interleukin-6 receptor antagonists—that could potentially treat symptoms of COVID-19. How does this work?

GC: I heard all the details of this trial. This is a realized trial with tocilizumab. Tocilizumab is an anti IL-6 drug that is used for management of graft versus host reaction in transplanted patients. There is a trial ongoing. We don't have data to tell you if it is working or not.

But in any case, the trial completed the accrual and the data will be analyzed.

Right.

GC: Then, we have other trials ongoing in Italy. The trials ongoing are with the antiretroviral therapy that actually is used for treatment of HIV—those are anti-HIV drugs. Then, we also have a trial ongoing with chloroquine and azithromycin. It is exactly the same trial ongoing in France—an antimalarial drug plus an antibiotic drug.

What is the scientific question these trials are designed to answer?

GC: The primary aim is to treat patients with pneumonitis that is related to an increase of IL-6, a massive cytokine storm related to the activation of the immune system against the virus. The hypothesis is, if you use a drug against IL-6, you reduce the cytokine storm, and you have an improvement of pneumonitis.

Since we last spoke, I'm sure you've seen that the United States is now number one in terms of coronavirus cases in the world.

GC: As we anticipated.

Yes. You saw this coming a few weeks ago, because it seemed like our situation was going to get worse than Italy's—and it currently is. What do you think went wrong?

GC: You know, I believe that the president of the United States decided not to start with social isolation and containment as soon as possible, despite Professor Anthony Fauci, the primary advisor for the president, suggesting that he do this. There is a disconnect between the political decision and scientific advice—because you have the best advisor in the world to control this infection and the COVID-19 spread.

Despite this, political decisions are not going in the right direction. The problem, as it was in Italy, is the balance between the economy and the potential economic crisis related to the spread—and scientific advice. That was very clear, also, in the United States.

This is the reason why you have spreading, dramatic spreading of the virus. I believe you should do a clear communication with *The Cancer Letter*. There is a solution to the spread, and this has been demonstrated in China. It is going to be demonstrated in Italy. The only solutions are not drugs or clinical studies. The only solutions are social isolation and containment—containment in the areas where you have a lot of people infected.

The first thing is to contain the state of New York, because it's dramatic, the situation in New York. I know from many friends that are working in clinical practice that there is shortage of personal protective equipment, there is shortage

of ventilators, and they are starting to do triage for patients. Who should we propose for intensive care units? They need to select the patients. There is a selection according, of course, to performance status, to age, comorbidities. They will not have the opportunity to access the intensive care unit for all the patients.

Is this happening already? This triaging of patients based on comorbidities?

GC: Yes, in the United States, I know because I read the tweets of all the medical doctors. They are starting to select patients, absolutely—and also in *The New York Times*.

The lack of personal protective equipment is a really big problem. The government also hasn't enforced social isolation to the same extent as Italy. Based on that, do you see the curve flattening in the U.S. at any point soon?

GC: No. You are rising. On the horizon, I don't see this curve flattening. You are 50 states—any state with a specific local governor will decide what to do and what not to do. I believe you will have 50 curves that will be completely different in the country—at different times.

The problem now is New York City, I believe. You need to invest a lot there, because millions of people are living there. I expect that many people are also dying and you don't know that they are COVID-19 positive. This is the reason.

I read that a young woman arrived in the hospital in the U.S. with no insurance—so she did not have access to an intensive care unit, and she died. In my country, we have a nationalized health system, and we reduced everything. We have clear numbers. We know how many people are dying, because we are transparent.

I don't know if you will register all the people who will die in the United States. Anthony Fauci predicted from 100,000 to 200,000 people that will die, and also President Trump says this. It's important, now, to offer care to all the people that need care, including people with no type of access to insurance. It's very important.

It is very concerning. Is there anything else you'd like to add?

GC: As a reporter, it is important to raise the big problem of personal protective equipment. As you know, also in Italy, we have many doctors who are positive. As I said previously, close to 10,000 health professionals actually are positive in Italy.

It's important in the United States to avoid this. If you have many doctors who are positive, they will spread the virus in the hospital and outside the hospital. The second point is to stress this concept of social isolation and containment. Now is the time to save lives—and then the economy will start again. You are a big country, and it will start again.

We had also a problem with personal protective equipment, so the situation was quite similar to the ones you are living now in the United States. Actually, there are 10,007 health care profes-

sionals infected in Italy. Seventy one doctors have died.

And these were primarily family doctors; right?

GC: They are half nurses and half family doctors. Yes.

Thank you so much for speaking with me today. It's hopeful to hear that the curve is flattening in Italy.

GC: Now in Spain, the situation is so severe. In Spain, in three weeks, they had 10,348 dead. Consider that our numbers now are actually from two months of spread. In Spain, in three weeks, they had as many cases in two weeks that we had in three months. It's dramatic.

It's very upsetting. Thank you again for taking the time to speak with me.

GC: Stay safe. Thank you, be careful.

Yes, you as well. I'll check in next week.

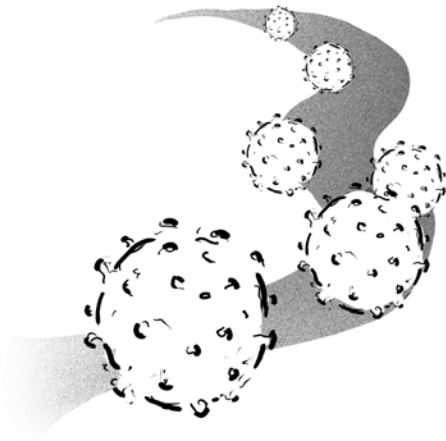
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COVID-19 UPDATES



AACR to Congress: Act on PPE, ventilator and testing shortages

The American Association for Cancer Research board of directors sent the following letter to congressional leadership March 30.

“Dear Speaker Pelosi, House Majority Leader Hoyer, House Minority Leader McCarthy, Senate Majority Leader McConnell, and Senate Minority Leader Schumer:

“As members of the Board of Directors of the American Association for Cancer Research, on behalf of the more than 47,000 laboratory, translational, and clinical researchers; physicians and other healthcare professionals; population scientists; and patient advocates who constitute our national and international membership, we applaud your tireless efforts to address the COVID-19 national health emergency, which include your recent passage of the historic \$2 trillion ‘Coronavirus Aid, Relief, and Economic Security Act’ (the ‘relief, recovery, and stimulus’ bill) to address the economic fallout from the

COVID-19 pandemic and provide vital emergency funding for hospitals and other essential elements of our nation’s healthcare infrastructure.

“Cancer researchers are at the forefront of biomedical research in the development of molecular diagnostics and therapeutics, and there is a convergence of coronavirus biology with cancer research that will have clinical importance. As the first and largest organization dedicated to the prevention and cure of all cancers through research and patient care, the AACR has the ability to marshal its members’ expertise and broad experience to aid the national COVID-19 response.

“The scientific and clinical knowledge of AACR members positions us to contribute in a major way to the deployment of resources and the advancement of research to overcome this pandemic. Time is of the essence, and we call on you and your colleagues in Congress to move swiftly forward to take the following steps to alleviate the COVID-19 public health emergency, while also ensuring patients with cancer are protected and the cancer workforce remains vibrant.

“Urge President Trump to use his powers to immediately and fully implement the Defense Production Act to direct industries to accelerate the manufacture of all the crucial medical equipment desperately needed to protect our frontline healthcare providers and to save the lives of those suffering from COVID-19.

“It is absolutely critical that we equip our healthcare providers currently entrenched in a ‘medical war zone’ with the personal protective equipment that is necessary to keep them, their families, and others safe, such as surgical and N95 masks, gloves, gowns and face shields.

“In addition, we implore you to take steps that provide critically ill patients with access to advanced life support systems, such as ventilators and ECMO devices. To this end, we strongly support the Medical Supply Chain Emergency Act, which was introduced on Monday, March 23, 2020, by Senators Chris Murphy (D-CN) and Brian Schatz (D-HI), as it calls on President Trump to use his powers to fully implement the DPA and produce 500 million masks as well as 200,000 ventilators and other desperately needed supplies including nasal swabs.

“Implement widespread testing of symptomatic individuals immediately, as well as asymptomatic individuals who have been exposed to infection or those in high-risk patient groups such as patients with cancer. Testing and tracking the novel coronavirus are vital measures to understanding the spread of COVID-19 in our communities, which will allow us to better isolate identified cases and contain the infection clusters that are present.

“Overly restrictive testing criteria, such as testing only those who had contact with an already infected individual or traveled to a specific foreign country, will not allow us to adequately assess and combat this rapidly advancing health crisis. Our healthcare providers should be able to access testing because they are on the front lines combatting this pandemic and are at increased risk of contracting and spreading this virus. It is also crucial to recognize that cancer treatment leaves many patients with compromised immune systems, placing them at increased risk for a severe, life-threatening case of COVID-19.

“Therefore, patients with cancer should be tested for COVID-19 whenever their oncologists or other healthcare providers deem it appropriate. Testing alone is not sufficient;

a de-identified, national central database should be established immediately to track novel coronavirus positive cases and those who are antibody positive, i.e., who have been exposed to the virus and developed immunity.

“Continue a nationwide social distancing policy for as long as necessary to reduce COVID-19 disease incidence and overall death toll, effectively protecting our frontline healthcare providers. Pulling back or even pausing our social distancing efforts prematurely would likely result in tens of thousands of additional cases and overwhelm our healthcare system. It is imperative that current social distancing policies be extended as required to end this national emergency.

“Uphold the rigorous, science-based approach of the U.S. Food and Drug Administration in its approval of all COVID-19 therapies. It is essential that the administration protect the agency’s high standards of safety and efficacy when approving COVID-19 therapies. We appreciate the rapid issue of guidance to industry, ‘Coronavirus (COVID-19) Update: FDA Issues Guidance for Conducting Clinical Trials,’ which prioritizes the safety of patients enrolled in clinical trials and provides insight into how to move forward with clinical trials already underway. The agency should continue to be open to well-designed, collaborative, innovative clinical trial strategies that will expedite the prevention, detection, and treatment of COVID-19.

“Encourage the use of the FDA’s expanded access program, sometimes referred to as ‘compassionate use’ as the primary pathway for patients to access investigational medical products and urge the agency to immediately deploy a COVID-19 focused version of Project Facilitate. Project Facilitate is an innovative, common sense, single point of contact program

that helps healthcare providers navigate expanded access for oncology therapeutics administered by the FDA Oncology Center of Excellence. Importantly, expanded access allows us to learn from the experience of every patient treated with investigational drugs, knowledge that will be vital for the conquest of COVID-19.

“Provide the telehealth digital infrastructure and technology needed to ensure continuity of care for patients with cancer. During the COVID-19 pandemic, telehealth technology will be especially valuable to enable vulnerable patients to receive some of their care at home and avoid exposure to the novel coronavirus when visiting the clinic. The survival of patients with cancer depends on the continuity of access to care.

“Although patients with cancer are immune-compromised and at high risk of severe COVID-19 disease, their cancer treatment cannot be interrupted indefinitely without dire health consequences. The expansion of telehealth programs will help patients with cancer by facilitating regular communication with providers and enabling access to timely information about their care. As telehealth is implemented more broadly, we urge you to incorporate patient privacy safeguards into any associated policies.

“Leverage the brain trust of cancer researchers and oncology healthcare providers who are contributing to our national capacity to address COVID-19. Cancer researchers are serving the global and national interest by lending their scientific and clinical expertise to address the COVID-19 pandemic.

“AACR members have the ability to drastically impact current efforts in diagnostic and treatment strategies. They are already working to

address coronavirus testing shortages by repurposing their laboratory space to make COVID-19 testing kits and are collecting and analyzing data on patients with cancer and COVID-19 through initiatives such as the COVID-19 and Cancer Consortium.

“Cancer researchers are able to leverage their laboratory expertise and capacity in numerous ways including to: aid in drug screening, development, and repurposing; develop antibody tests; investigate the efficacy of convalescent serum from recovered COVID-19 infected persons as treatment; and conduct vaccine research for COVID-19. Clinical cancer researchers are also well positioned to help manage aspects of care for COVID-19 patients.

“Through the study and use of new immunotherapies, including CAR T-cell therapies, cancer researchers have gained experience using immune-modulating therapies and managing severe immune-mediated side effects also seen in COVID-19. Serious consideration should be given to engaging cancer researchers from various disciplines, oncology healthcare providers, and laboratory professionals in a call to action to study, detect, and defeat COVID-19. The AACR is prepared to survey its constituents to identify volunteers who are willing to help conduct COVID-19 testing during this time when research laboratories are not functioning.

“Continue your exceptional support and steadfast commitment to cancer and medical research. During the past five years, you have prioritized funding for NIH to the point that the agency’s budget has increased by \$11.6 billion or 39%. The COVID-19 pandemic highlights the importance and value of the NIH portfolio, and emphasizes that this generous support must be sustained, even more so during this

period when our nation is facing a national health emergency.

“The support you have shown for cancer and medical research has contributed to a substantial reduction in cancer incidence and mortality. The age-adjusted U.S. cancer death rate declined by 29% from 1991 to 2017, a reduction that translates into 2.9 million cancer deaths avoided. Therefore, during the fiscal year 2021 appropriations process, we will be calling on you to help make sure this scientific progress continues.

“The future of cancer and medical research depends on ensuring career continuity for researchers despite the adverse influences of COVID-19. Diminished research time and output due to the COVID-19 crisis will unduly harm less-established investigators when they apply for grants.

“This professional uncertainty is compounded by financial insecurity, as many early-career scientists struggle with considerable student loan debt. We appreciate the support you have shown in the passage of the relief, recovery, and stimulus bill to help Americans who are struggling to repay their student loans. We ask that you consider additional measures that will encourage these vulnerable scientists to persist in their research careers, such as directing the NIH to extend the duration of grants to accommodate research disruptions caused by COVID-19 and modifying eligibility windows for special career stage designations (e.g., postdoc and early-stage investigator).

“Sustain scientific innovation and progress for the benefit of patients and cancer survivors. We have serious concerns about the toll that economic stress resulting from the COVID-19 public health challenge is taking on scientific innovation. Assurances from

NIH Deputy Director for Extramural Research Michael Lauer and NCI Director Ned Sharpless that NIH and NCI peer review and grants administration will continue as previously scheduled are encouraging.

“However, while a focus must be maintained on conquering COVID-19, a prolonged halting of our national cancer research efforts will slow the recent rate of progress in providing patients with new therapies for cancer. Unfortunately, the current COVID-19 crisis is resulting in cancer clinical trials grinding to a halt, and healthcare and PPE shortages have a deleterious effect on all areas of cancer research and patient care. When this global pandemic is behind us, Congress must provide the necessary resources to maximize the potential for future advances in cancer and medical research and treatment.

“Promoting innovation through the dissemination of new cancer research findings among scientists and other stakeholders is at the core of the AACR mission, and rapid communication of the latest developments in science and medicine is now more important than ever. Therefore, effective immediately, the AACR is making any journal article containing information directly relevant to advancing our understanding of COVID-19 open access and available online. Further, we are already hard at work conducting web-based conferences, and we will organize sessions at our scientific meetings that address the biologic and clinical intersection of COVID-19 and cancer.

“In conclusion, your leadership and support over the past several decades have ensured the development of a highly effective National Cancer Program that can now apply its unique and substantive knowledge and skills to help society defeat this

virulent pathogen. We recognize the need to take action immediately to vanquish this virus that threatens the lives of millions of Americans, ravages our economy, and derails scientific progress. Otherwise, our healthcare system will fail and our most vulnerable patients, including those with cancer, will disproportionately suffer. The AACR and its members stand ready to work with you and other members of Congress to achieve the vital recommendations set forth herein. Thank you in advance for your consideration.”

Advocacy organizations: Stop threatening health care workers who speak out about lack of PPE

In a public letter to the American Hospital Association, [54 health care organizations](#) condemned attempts by hospital administrators to muzzle health care workers who speak out against coronavirus caseloads and supply shortages.

The letter, dated March 27, follows:

“We were appalled to read recent media reports about hospital administrators across the U.S. muzzling doctors, nurses, and other healthcare professionals with threats of disciplinary action for speaking out about coronavirus patient caseloads and dwindling hospital supplies needed to care for such patients.

“It is critical that the public and local, state, and federal government officials fully comprehend the scope of shortages of personal protective equipment, mechanical ventilators, intensive care unit beds, and other

medical supplies so that appropriate steps can be taken to mitigate shortages of these essential medical resources, appropriately and fairly allocate limited resources, and thus protect the safety and welfare of health care workers and patients alike. Attempts to cover up these shortages by muzzling health care workers who are on the front lines of fighting the COVID-19 pandemic are reprehensible and reckless and endanger public health.

“Although such actions may be commonplace in countries with authoritarian regimes, they are not acceptable in the U.S. The undersigned consumer advocacy, workers’ rights, science, research, public health, civil rights, human rights, and grassroots political organizations, labor unions, and individuals therefore demand that the American Hospital Association publicly denounce any such efforts to muzzle health care professionals and call on its member hospitals and health care systems to encourage their doctors, nurses, and other health care professionals to speak freely about coronavirus patient caseloads, dwindling hospital supplies, and any other challenges that should be immediately addressed.

“Thank you for your prompt attention to this urgent public health matter. Please contact Dr. Michael Carome, Director of Public Citizen’s Health Research Group, at mcarome@citizen.org with your response.”

American College of Surgeons: Health care workers need PPE

The following is a statement from the American College of Surgeons.

“The American College of Surgeons recognizes that many healthcare facilities are facing shortages of personal protective equipment, including face masks, gowns, and respirators. The ACS believes it is essential that surgeons, nurses, anesthesiologists, and other health care personnel be able to speak freely, without fear of retribution, as they seek to find a solution to accessing PPE. We advise surgeons to speak with their institutional leadership on these matters and to be able to direct any concerns to the ACS, with the goal of protecting themselves and their colleagues.

“The Joint Commission has released a statement supporting the use of standard face masks and respirators provided from home when health care facilities cannot provide access to PPE that is commensurate with the risk to which health care personnel are exposed during the COVID-19 pandemic. Where masks or respirators are recommended, the ACS maintains that surgeons should have access to and latitude to wear these masks at their sole discretion. The Centers for Disease Control and Prevention also has released a document that offers a series of strategies or options to optimize supplies of disposable N95 filtering facepiece respirators.

“The ACS strongly supports the ability of surgeons to use their own masks or other PPE, but this option does not obviate the hospital’s responsibility to provide adequate PPE to all their health care workers. In these extraordinary times, the ACS encourages institutions to adapt and be flexible so that health care personnel continue to feel safe; The Joint Commission guidelines are a reasonable starting point.”

CPRIT suspends first cycle of awards for FY21

Cancer Prevention and Research Institute of Texas has suspended its first cycle of grant applications for fiscal year 2021 for Academic Research, Product Development Research and Prevention Program awards.

CPRIT is taking this action in response to the unexpected impact to the budget from the COVID-19 pandemic and a projected decrease in oil and gas revenues. CPRIT continues to evaluate releasing Requests for Applications for fiscal year 2021 and is committed to doing so if circumstances support it.

CPRIT has closed the FY 21.1 Academic Research Program RFAs listed below (originally due June 3). CPRIT will not accept applications responding to these RFAs and will withdraw any FY 21.1 applications already submitted.

Applications for the second cycle of fiscal year 2020 (FY 20.2) are undergoing peer review. CPRIT is not withdrawing the FY 20.2 applications and expects to announce awards in August or early fall.

- RFA R-21.1 - RTA Research Training Awards
- RFA R-21.1 - IIRA Individual Investigator Research Awards
- RFA R-21.1 - IIRACCA Individual Investigator Research Awards for Cancer in Children and Adolescents
- RFA R-21.1 - IIRACT Individual Investigator Research Awards for Clinical Translation
- RFA R-21.1 - IIRACSBBC Individual Investigator Research Awards for Computational Systems Biology of Cancer

- RFA R-21.1 - IIRAP Individual Investigator Research Awards for Prevention and Early Detection

Scott Gottlieb: A road map for navigating COVID-19 in the U.S.

In a report published by the American Enterprise Institute, former FDA Commissioner Scott Gottlieb proposes a road map for navigating COVID-19 in the United States.

Gottlieb's report identifies four phases and the related actions which need to be taken by those overseeing America's public health strategy to bring the spread of COVID-19 under control and to transition slowly to next steps leading to reopening the country.

Gottlieb co-authored the report with the following public health experts: Mark McClellan, MD, PhD; Caitlin Rivers, PhD, MPH; Lauren Silvis, JD; and Crystal Watson, DrPH, MPH.

Read the full report [here](#).

The authors outline the following four phases:

Phase I: Slow the Spread - Break off the chain of epidemic transmission

- Measures like social distancing will need to be in place nationally until transmission has slowed down and health infrastructure can be scaled up to safely manage the outbreak.

Phase II: Reopen, State by State - Gradually shift to a focus on individual cases versus entire populations

- States can move to phase II when they are able to safely diagnose,

treat, and isolate COVID-19 cases and their contact

- Self-distancing measures will still need to be in place to prevent transmission from accelerating again (such as increased distancing in lines, elevators, and indoor spaces).
- Deep cleaning (sanitizing) of shared spaces should become routine.
- Initially the public will be asked to limit their gatherings, and people will initially be asked to wear face masks while in the community in order to reduce their risk of asymptomatic spread

Phase III: Establish Protection Then Lift All Restrictions- Effective therapeutics, widespread screening and surveillance, and a vaccine

- Physical distancing restrictions and other Phase II measures can be lifted only when we have available to us safe and effective technology for mitigating the risk of COVID-19.
- This technology includes: broad based surveillance, therapeutics that can rescue patients with significant disease, or prevent serious illness in those most at risk, and/or a safe and effective vaccine

Phase IV: Rebuild Our Readiness for the Next Pandemic

- We must build the tools and systems to ensure that we are never again unprepared to face a new infectious disease threat as soon as we successfully defeat COVID-19.
- Preparedness for public health emergencies should be elevated as a function in the White House, with a coordinating function equivalent to the Director of National Intelligence

CMS addresses surge of COVID-19 patients

The Centers for Medicare & Medicaid Services March 30 issued regulatory waivers and new rules to respond to the 2019 novel coronavirus pandemic.

These temporary changes will apply immediately across the U.S. healthcare system for the duration of the emergency declaration. This allows hospitals and health systems to deliver services at other locations to make room for COVID-19 patients needing acute care in their main facility.

The changes allow local hospitals and healthcare systems to expand treatment capacity that allows them to separate patients infected with COVID-19 from those who are not affected.

CMS recently approved hundreds of waiver requests from healthcare providers, state governments, and state hospital associations in the following states: Ohio; Tennessee; Virginia; Missouri; Michigan; New Hampshire; Oregon; California; Washington; Illinois; Iowa; South Dakota; Texas; New Jersey; and North Carolina. Other states and providers do not need to apply for these waivers and can begin using the flexibilities immediately.

CMS's temporary actions allow local hospitals and healthcare systems to:

Increase hospital capacity:

- Communities can use local ambulatory surgery centers that have canceled elective surgeries, per federal recommendations. Surgery centers can contract with local healthcare systems to provide hospital services, or they can enroll and bill as hospitals during the

emergency declaration as long as they are not inconsistent with their state's Emergency Preparedness or Pandemic Plan. The new flexibilities will also leverage these types of sites to decant services typically provided by hospitals such as cancer procedures, trauma surgeries and other essential surgeries.

- CMS will now temporarily permit non-hospital buildings and spaces to be used for patient care and quarantine sites, provided that the location is approved by the State and ensures the safety and comfort of patients and staff. This will expand the capacity of communities to develop a system of care that safely treats patients without COVID-19, and isolate and treat patients with COVID-19.
- CMS will also allow hospitals, laboratories, and other entities to perform tests for COVID-19 on people at home and in other community-based settings outside of the hospital. The new guidance allows healthcare systems, hospitals, and communities to set up testing sites exclusively for the purpose of identifying COVID-19-positive patients in a safe environment.
- CMS will allow hospital emergency departments to test and screen patients for COVID-19 at drive-through and off-campus test sites.
- During the public health emergency, ambulances can transport patients to a wider range of locations when other transportation is not medically appropriate. These destinations include community mental health centers, federally qualified health centers, physician's offices, urgent care facilities, ambulatory surgery centers, and any locations furnishing dialysis services when an ESRD facility is not available.

- Physician-owned hospitals can temporarily increase the number of their licensed beds, operating rooms, and procedure rooms. For example, a physician-owned hospital may temporarily convert observation beds to inpatient beds to accommodate patient surge during the public health emergency.
- Hospitals can bill for services provided outside their four walls. Emergency departments of hospitals can use telehealth services to quickly assess patients to determine the most appropriate site of care, freeing emergency space for those that need it most. New rules ensure that patients can be screened at alternate treatment and testing sites which are not subject to the Emergency Medical Labor and Treatment Act as long as the national emergency remains in force. This will allow hospitals, psychiatric hospitals, and critical access hospitals to screen patients at a location offsite from the hospital's campus to prevent the spread of COVID-19.

Expand the healthcare workforce:

- Local private practice clinicians and their trained staff may be available for temporary employment because nonessential medical and surgical services are postponed during the public health emergency. CMS's temporary requirements allow hospitals and healthcare systems to increase their workforce capacity by removing barriers for physicians, nurses, and other clinicians to be readily hired from the local community as well as those licensed from other states without violating Medicare rules.
- These healthcare workers can then perform the functions they are qualified and licensed for, while awaiting completion of federal paperwork requirements.

- CMS is issuing waivers so that hospitals can use other practitioners, such as physician assistants and nurse practitioners, to the fullest extent possible, in accordance with a state's emergency preparedness or pandemic plan. These clinicians can perform services such as order tests and medications that may have previously required a physician's order where this is permitted under state law.
- CMS is waiving the requirements that a certified registered nurse anesthetist is under the supervision of a physician. This will allow CRNAs to function to the fullest extent allowed by the state, and free up physicians from the supervisory requirement and expand the capacity of both CRNAs and physicians.
- CMS also is issuing a blanket waiver to allow hospitals to provide benefits and support to their medical staff, such as multiple daily meals, laundry service for personal clothing, or child care services while the physicians and other staff are at the hospital and engaging in activities that benefit the hospital and its patients.
- CMS will also allow healthcare providers (clinicians, hospitals and other institutional providers, and suppliers) to enroll in Medicare temporarily to provide care during the public health emergency.

Reducing paperwork:

- CMS is temporarily eliminating paperwork requirements and allowing clinicians to spend more time with patients. Medicare will now cover respiratory-related devices and equipment for any medical reason determined by clinicians so that patients can get the care they need; previously Medicare only covered them under certain circumstances.

- During the public health emergency, hospitals will not be required to have written policies on processes and visitation of patients who are in COVID-19 isolation. Hospitals will also have more time to provide patients a copy of their medical record.
 - CMS is providing temporary relief from many audit and reporting requirements so that providers, healthcare facilities, Medicare Advantage health plans, Medicare Part D prescription drug plans, and states can focus on providing needed care to Medicare and Medicaid beneficiaries affected by COVID-19.
 - This is being done by extending reporting deadlines and suspending documentation requests which would take time away from patient care.
- established patients now may stay at home and have a telehealth visit with their provider.
- CMS is allowing telehealth to fulfill many face-to-face visit requirements for clinicians to see their patients in inpatient rehabilitation facilities, hospice and home health.
 - CMS is making it clear that clinicians can provide remote patient monitoring services to patients with acute and chronic conditions, and can be provided for patients with only one disease. For example, remote patient monitoring can be used to monitor a patient's oxygen saturation levels using pulse oximetry.
 - In addition, CMS is allowing physicians to supervise their clinical staff using virtual technologies when appropriate, instead of requiring in-person presence.

Promote telehealth in Medicare:

- Building on prior action to expand reimbursement for telehealth services to Medicare beneficiaries, CMS will now allow for more than 80 additional services to be furnished via telehealth. During the public health emergencies, individuals can use interactive apps with audio and video capabilities to visit with their clinician for an even broader range of services. Providers also can evaluate beneficiaries who have audio phones only.
- These temporary changes will ensure that patients have access to physicians and other providers while remaining safely at home.
- Providers can bill for telehealth visits at the same rate as in-person visits. Telehealth visits include emergency department visits, initial nursing facility and discharge visits, home visits, and therapy services, which must be provided by a clinician that is allowed to provide telehealth. New as well as

COA thanks CMS for telehealth expansion

The following is a statement from Ted Okon, executive director of the Community Oncology Alliance, on recent CMS expansions in light of COVID-19.

“The Community Oncology Alliance applauds the Centers for Medicare & Medicaid Services for new flexibilities to telehealth regulations and rules that will allow community oncology providers to dramatically expand safe cancer treatment during the COVID-19 global pandemic. This major expansion of telehealth services and relaxation of regulations provides a huge boost to the ability of community practices to care for patients with cancer whose treatment cannot stop.

“The new regulatory relief and rules from CMS are extensive and include

the ability for providers to furnish 80 more services via telehealth and to bill for telehealth visits at the same rate as in-person visits. Additionally, CMS has made it clear that providers can now evaluate patients who have audio-only phone systems, an immense easing of burdens for those patients who might not have access to, or are not comfortable with, advanced technology.

“The COVID-19 pandemic has forced a major reorganization and restructuring of cancer care in America. CMS' rapid response to the crisis in recent weeks means that patients with cancer, many of whom are Medicare seniors with compromised immune systems that are most at risk of infection, can continue to receive cancer treatments while staying safe.

“For example, thanks to telehealth, a community oncology practice in Oregon has been able to treat an 81-year-old patient with a new diagnosis of acute myeloid leukemia. That person is being managed remotely, with labs drawn at the patient's residence center. Weekly virtual telehealth meetings allow the physician to track how the patient is doing, ensuring they receive needed cancer care in a safe, cost-efficient setting.

“A community oncology practice in North Texas also reports that telemedicine is allowing it to spare rural patients with long drives into urban areas that have seen COVID-19 outbreaks. This is not only reducing lengthy travel times but also greatly reduces their risk of exposure to the virus. Just this week, because of the new Medicare telehealth policies, the practice has been able to help a new patient with liver disease avoid a 133-mile drive as well as coordinate with other specialists for their cancer care.

“Community oncology can’t thank CMS and Administrator Seema Verma enough for quickly moving these changes forward that will dramatically help oncology providers diagnose and monitor their patients safely during the COVID-19 pandemic. CMS has demonstrated an amazing ability to cut through the red tape of Medicare bureaucracy and speed up these critically important changes. They are right on target in providing a veritable lifeline to Americans who are struggling with cancer in the midst of crisis.

“Across the country, independent community oncology practices have risen to the challenge of the COVID-19 pandemic and continue to serve as cancer care providers for millions of patients. As the providers of cancer care to the majority of patients in America, now more than ever, it is crucial that community oncology practices stay open and active for patients as cancer and cancer care do not stop during times of national emergencies. The expansion of telehealth options and reduction of regulatory burdens are important steps that allow practices to do that while also keeping patients safe and healthy.”

LLS, partners commit \$4.5M for blood cancer patients impacted by COVID-19

The Leukemia & Lymphoma Society and its partners developed the [LLS COVID-19 Patient Financial Aid Program](#) to provide \$250 for eligible blood cancer patients struggling with the economic hardship because of COVID-19.

Amgen, Inc., Bristol Myers Squibb Foundation, Foundation Medicine, Inc., Ge-

nentech, a member of the Roche Group, Incyte, MorphoSys Foundation, Servier Pharmaceuticals, Subaru of America, Inc., and Takeda Oncology are contributing to the program.

“Along with our partners, we anticipated that blood cancer patients would need help with non-medical expenses such as food and other household needs, and housing and transportation,” Louis J. DeGennaro, LLS president and CEO, said in a statement. “And we aim to raise up to \$10 million to help even more patients during this crisis.”

LLS is providing free educational resources and support to patients through a series of blogs, webinars and chats led by medical professionals.

LLS is soliciting [donations](#) for the program. All donations contribute to LLS’s mission to find cures for blood cancers and to ensure patient access to care.

PharmaMar submits phase II clinical trial of Aplidin treatment of COVID-19 to the Spanish Medicines Agency

The APLICOV clinical trial protocol for Aplidin (plitidepsin) was submitted to the Spanish Medicines and Healthcare Products Agency.

PharmaMar sponsors the multicenter, randomized phase II clinical trial, in which two different doses of plitidepsin will be evaluated for the treatment of patients with COVID-19 pneumonia. The protocol is currently being evaluated.

The protocol includes 160 patients admitted to hospitals in Spain, where it is intended to assess whether plitidepsin, administered intravenously for 5 days

to patients with COVID-19 pneumonia, reduces the proportion of patients who progress to Acute Respiratory Distress Syndrome, the main cause of patients requiring mechanical ventilation and/or admission to intensive care units.

Several Spanish centers are due to participate in the study and which is expected to start as soon as the authorization from the health authorities is obtained.

On March 13, PharmaMar announced the results of in vitro studies of plitidepsin in human coronavirus HCoV-229E, with a mechanism of multiplication and propagation that is very similar to that of SARS-CoV-2. The studies were carried out at the National Biotechnology Centre of the Spanish National Research Council by Luis Enjuanes, Sonia Zúñiga and Isabel Solá.

“As soon as we receive authorization from the AEMPS, we will be able to start the clinical trial with plitidepsin and we hope that it can become an effective weapon against COVID-19,” José María Fernández, president of PharmaMar, said in a statement.

Plitidepsin acts by blocking the protein eEF1A, present in human cells, which is used by SARS-CoV-2 to reproduce and infect other cells. By means of this blocking, the reproduction of the virus inside the cell is prevented, making its propagation to the rest of the organism’s cells, not feasible.

Study: Patients with new-onset digestive symptoms after possible COVID-19 contact should be suspected for the illness

A unique subgroup of patients who have COVID-19 with low severity dis-

ease experienced digestive symptoms, most notably diarrhea, according to a study published in *The American Journal of Gastroenterology*.

The authors, from Union Hospital and Tongji Medical College in Wuhan, China, report that these digestive ailments presented themselves as early symptoms of COVID-19 in some patients.

“This study is vital because it represents the 80% or more of patients who do not have severe or critical disease,” Brennan M.R. Spiegel, co-editor-in-chief of *The American Journal of Gastroenterology*, said in a statement. “This is about the more common scenario of people in the community struggling to figure out if they might have COVID-19 because of new-onset diarrhea, nausea, or vomiting.”

The analysis included 206 patients with low severity COVID-19, including 48 presenting with a digestive symptom alone, 69 with both digestive and respiratory symptoms, and 89 with respiratory symptoms alone.

Key Findings:

- There is a unique subgroup of COVID-19 patients with low severity disease marked by presence of digestive symptoms.
- These patients are more likely to test positive in stool for COVID-19 RNA, to have a longer delay before viral clearance, and to experience delayed diagnosis compared to patients with respiratory symptoms but no digestive symptoms.
- In some cases, the digestive symptoms, particularly diarrhea, can be the initial presentation of COVID-19, and may only later or never present with respiratory symptoms or fever.
- Importantly, only two-thirds of people in this study had a fever, mean-

ing it is not even necessary to have a fever to suspect the diagnosis.

- These data emphasize that patients with new-onset digestive symptoms after a possible COVID-19 contact must be suspected for the illness, even in the absence of cough, shortness of breath, sore throat, or fever.

Convalescent plasma donations to be collected by Versiti Blood Centers to treat COVID-19 patients

Versiti Inc. in early April plans to collect plasma from recovered COVID-19 patients to help treat others with the virus.

The blood-related treatment—approved by the FDA as an Emergency Investigational New Drug—would be used by hospitals for the most severely affected patients.

Versiti blood centers is working with partner hospitals to identify recovered patients. As per the guidelines, hospitals must request FDA approval and work within the EIND guidelines, or other approved IND, in order to treat coronavirus patients with plasma. Donors would be referred to Versiti through hospitals, or the recovered patients’ physicians.

“The potential donors must first be proven to have had a COVID-19 diagnosis through a positive lab test result, and must then have a negative test result 14 days after recovering from symptoms,” Versiti Senior Medical Director Dan A. Waxman said in a statement. “It’s a very collaborative effort with our hospital partners who will be working to identify and verify the donors.”

Versiti hopes to implement the coronavirus plasma collection program in early April. The donated plasma will be provided directly to the hospitals with whom Versiti is partnering.

“Many of our hospital partners have already requested the donations,” Waxman said. “They are anxious to begin the program.”

The plasma treatment would transfer the antibodies that the recovered patient created into critically ill patients currently receiving care. Because of the investigational nature of this treatment, it is difficult to know just how many plasma infusions a COVID-19 patient may require, Waxman said.

Plasma donations take about 30 to 40 minutes and will be collected at Versiti donor centers in Illinois, Indiana, Michigan, Ohio and Wisconsin. The donation process is the same as with other plasma donations, and will be performed using an apheresis machine.

Though blood group AB is the universal plasma donor, any blood type donor who has recovered from the virus is eligible to donate as part of the program.

Versiti is working with Froedtert Hospital and the Medical College of Wisconsin, under the direction of Gilbert White, Versiti executive vice president for research and chief science officer and professor at MCW, who is serving as the primary investigator, and Mary Beth Graham, medical director of Infection Prevention & Control at Froedtert Hospital, and associate chief of the Division of Infectious Disease at MCW, to support a research study related to plasma infusion.

“This is a very important joint effort that we are undertaking which will benefit every hospital system in the state of Wisconsin and beyond,” White said.

The research project involves a clinical trial component with recovered coronavirus patients, who will be referred by hospitals.

Metastatic breast cancer patient tests negative for COVID-19

Janice Cowden, a Florida resident who has metastatic breast cancer and symptoms of the novel coronavirus, has tested negative for COVID-19 after a lengthy process that involved being denied testing multiple times—despite her vulnerable status (*The Cancer Letter*, [March 20](#)).

Cowden, 62, was worried about having potentially exposed other patients at a fundraising event in late February. Two weeks ago, on March 21, she finally received a test. To be exact, she received two tests—one at a curbside testing facility, and one at her primary care provider.

It took 13 days for Cowden to receive the results from both tests. “The upside of two negative tests is that MD Anderson might be less likely to reschedule my PET/CT/Onc appointments again,” Cowden said.

Cowden’s symptoms have mostly subsided after a full month of not knowing whether she put others at risk. The delay indicates a nationwide response to COVID-19 that can be best described, in Cowden’s words, as “a total shit show.”

“That’s usually what we call metastatic breast cancer—just a total shit show. It’s very valid to use that term in relation to this virus too, because it truly is that,” Cowden said.

Cowden first developed symptoms of COVID-19 in early March—severe coughing, labored breathing, aches and a high fever of 103. There was a delay in testing, because her primary care physician and the emergency room didn’t have any tests.

“This whole experience has been one of extreme frustration and disappointment for me. There are so many other people who are just at the beginning of this,” Cowden said. “Clearly they’re not going to be getting their results, unless they’re inpatient, any faster—or unless they’re a health care worker at a facility.”

In Florida, where there are upwards of 8,000 confirmed cases of the virus, Gov. Ron DeSantis issued a statewide stay-at-home order April 1. On the day Cowden sought treatment at the ER at the direction of her primary care physician, her community held a St. Patrick’s Day celebration.

“It’s just so widespread in Florida. So, I look at this and I think, why is it so difficult for Americans in general to do what we need to do to lessen the spread of the disease?” Cowden said. “Those of us who’ve been immunocompromised due to disease treatment for breast cancer are used to having to socially isolate. If they could just do it for a short time, then it would change that entire trajectory pattern.”

FAQs and Guidances

Federal government:

- NCI [source book and resources](#): clinical and laboratory operations
- 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).

- CTEP [coronavirus guidance](#)

- COVID-19 [scientific interest group](#)

- FDA [guidance](#): Conduct of clinical trials of medical products during COVID-19 pandemic

- FDA [guidance update](#): Blood donations

☞ 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

☞ [Update](#): Diagnostic testing for 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
- ◊ COVID-19 and 2020 ACS Grants
- 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

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THE CLINICAL CANCER LETTER



TRIALS & TRIBULATIONS

COVID-19 and cancer: Ethical dilemmas in immune checkpoint blockade



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As oncologists, we are all too familiar with making treatment recommendations and advising on end-of-life care in the absence of robust data. In ethical conundrums, we rely on guidance from our colleagues in the field, institutions, and national/international leadership bodies.

These decisions are even more urgent during the current COVID-19 pandemic. These are truly unprecedented times. While we certainly have faced

outbreaks of life-threatening illness before, few have been as prevalent and as virulent as the novel coronavirus.

The closest parallel we can draw is to the 1918 influenza pandemic, which swept rapidly around the world, leaving an estimated 50 million people dead. Though devastating, medical management in this past era was reasonably straightforward. There were no vaccines, no antibiotics, and few supportive care interventions available to patients.

Personal hygiene, thorough cleaning, and isolation—so-called “social distancing” in the modern vernacular—became the best interventions against the virus. As they are today, individuals with comorbid conditions such as cancer were likely at high risk for contracting and dying from influenza.

A key difference, however, is that in 1918, the field of oncology was in its infancy. Surgery was employed for localized disease when possible, and radi-

ation therapy with radium had recently been adopted. There were no options for systemic therapy. Thus, when the 1918 influenza pandemic struck, cancer patients and their doctors faced few management decisions surrounding how best to treat their cancer.

The remarkable therapeutic breakthroughs of the past century have yielded systemic treatment options for many patients with advanced cancer. Chemotherapy, targeted therapy, and now immunotherapy with immune checkpoint blockade, have all been incorporated into standard regimens for patients with cancer.

This relative abundance of therapeutic options has certainly improved outcomes for our patients. With each new therapeutic option comes new ques-



With each new therapeutic option come new questions about the risk of toxicity versus the expected benefit and concerns about appropriate use of limited resources. These are challenging questions at the best of times.



tions about the risk of toxicity versus the expected benefit and concerns about appropriate use of limited resources. These are challenging questions at the best of times.

The COVID-19 pandemic has magnified many of these ethical dilemmas and raised new and unexpected challenges. I will focus here on what I consider some of the key challenges during the COVID pandemic surrounding the use of immune checkpoint inhibitors, the fastest growing option for systemic therapy for a variety of malignancies.

When considering how to best care for our patients in these challenging times, we must come back to fundamental ethical principles. First, do no harm. While this is often a challenge for oncologists who need to consider toxicities from systemic therapy in the face of often a life-threatening cancer, this notion has taken on particular acuity during the COVID pandemic.

How should we view therapies that may treat the cancer but place the patient at higher risk of contracting, or having a more serious course with COVID-19, either as a result of immune suppression for treatment-related toxicities or, more directly, through higher baseline inflammation?

Do we delay therapy until we are past the peak of transmission, and there-

in take the risk of disease progression that we may or may not be able to control when treatment can be given more safely?

We know that immunotherapy comes with a risk of pneumonitis; could there be synergy between PD-1 inhibitor-induced pneumonitis and the inflammatory ARDS that can be lethal with COVID-19?

Taken further, might the proinflammatory state promoted by checkpoint inhibitors exacerbate COVID complications? Are these theoretical risks suffi-

cient to withhold potentially life-sustaining immunotherapy? Alternatively, might the immune enhancing nature of checkpoint inhibitors help to prevent COVID infection?

No one can definitively answer any of these questions. We must rely on our colleagues to help guide decisions in the absence of robust data.

With this in mind, nonetheless, I humbly put forth a few of my own guiding principles for your consideration.

1. To minimize risk of immune-mediated adverse events and therefore the need for immunosuppressive treatment, I suggest considering a PD-1-targeting regimen alone, as opposed in combination (i.e. nivolumab + ipilimumab), in the absence of clear evidence of superiority of a combination regimen (e.g. melanoma brain metastases).

Incremental benefit of combination regimens must be weighed heavily against the likelihood of requiring steroids or other immunosuppressive agents, which may increase the likelihood of contracting COVID-19 or diminish the patient's ability to clear the virus.

Similar considerations must be given to chemotherapy in combination with immunotherapy, as chemotherapy-induced immunosuppression could heighten risk of infection.

2. Fewer treatment sessions mean fewer opportunities for virus transmission from health care workers and other patients. This lowers risk for both patients and providers. Utilize available tools to extend time between treatment sessions.

For example, many oncologists continue to prescribe nivolumab 240 mg every 2 weeks, as opposed

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to the 480 mg every-4-week regimen, which has similar pharmacokinetic exposure over the 4 week period. Switching to the every-4-week regimen decreases the number of visits (and therefore, the risk of exposure at a health care facility) in half.

For patients with well-controlled disease (including low volume, stable stage IV), or those being treated with adjuvant immunotherapy, the risk of a health care visit may outweigh the benefit of a single dose.

For example, NCCN recently issued “Short-Term Recommendations for Cutaneous Melanoma Management During COVID-19 Pandemic” advocating for deferral of adjuvant therapy for patients with <50% estimated risk of disease relapse.

3. Given the risks, perhaps immunotherapy should be given only when the regimen has demonstrated some clinical activity. Truly novel agents or combinations should be discouraged. This is the most challenging of the proposed principles.

Often, patients with few treatment options wish to try cutting-edge therapies, either by compassionate use or on a clinical trial, despite little expected clinical benefit. I suggest that the known risks of immunotherapy and potential need for immunosuppression should drive our decisions during the time of the COVID pandemic.

Physicians must also balance the risk to themselves and other essential medical personnel needed to care for patients. I am not alone in this thinking, and many institutions have limited enrollment on clinical

trials to those that have demonstrated clear therapeutic benefit.

While it is difficult to give up hope that an unlikely therapy may benefit the patient, we know that the risk of severe illness with COVID-19 is high, particularly in patients with advanced cancer. If a clinical trial is being considered, we should prioritize those with oral dosing (versus intravenous, radiation, or procedure-based) and less frequent visits to minimize risk of exposure to patients and medical staff.

Undoubtedly, these are challenging times. Perhaps the most difficult times some of us will face in our careers. Many of us are struggling with decisions we hoped we would never have to make and some that we never even imagined. Here, I suggest some of my personal guiding principles when faced with challenging decisions about immunotherapy.

They are by no means comprehensive, but my hope is that they will provide a framework around which to approach therapeutic decisions. But the strength of our community is just that—community.

We are in this together, and my hope is that these suggestions spark more conversation and collaboration. Though you may be the one writing (or not writing) the order, you are not alone in making these difficult decisions. Now, more than ever, is the time to lean on each other for help and support.

CLINICAL ROUNDUP



Keytruda significantly improves PFS as first-line treatment in colorectal cancer indication

The phase III KEYNOTE-177 trial evaluating first-line treatment of Keytruda in patients with microsatellite instability-high or mismatch repair deficient unresectable or metastatic colorectal cancer met one of its dual primary endpoints of progression-free survival.

Merck sponsors Keytruda.

Based on an interim analysis conducted by an independent data monitoring committee, Keytruda monotherapy demonstrated a statistically significant and clinically meaningful improvement in PFS compared with chemotherapy (investigator's choice of mFOLFOX6 or FOLFIRI, with or without bevacizumab or cetuximab). Based on the committee's recommendation, the study will continue without changes to evaluate overall survival, the other dual primary endpoint. The safety profile of Keytruda in this trial was consistent with previously reported studies, and no new safety signals were identified.

"These head-to-head data with Keytruda are the first time a single-agent, anti-cancer therapy, and particularly an anti-PD-1 monotherapy, achieved a statistically significant improvement in progression-free survival over chemotherapy, including the current standard of care regimen of mFOLFOX6 plus bevacizumab, in patients with MSI-H colorectal cancer," Roy Baynes, senior vice president and head of global clinical development, and chief medical officer of Merck Research Laboratories, said in a statement.

In May 2017, Keytruda became the first cancer therapy approved by FDA for use based on a biomarker, regardless of tumor type, in previously treated patients with MSI-H or dMMR solid tumors.

Phase III cancer vaccine trial meets primary endpoint

The primary endpoint was met in a pre-defined step-1 analysis of a phase III trial in non-small cell lung cancer patients treated with Tedopi, a neoepitope cancer vaccine.

Data showed a 12 month-survival rate of 46% for patients treated with Tedopi versus 36% for patients in the chemotherapy control arm. Enrollment in the Step-2 portion of the phase III trial have been stopped due to concerns over COVID-19.

Instead, there will be further analysis of step-1 data in parallel with discussions with regulatory agencies on a pathway to approval.

Tedopi is being developed in a phase 3 trial in NSCLC for patients who have failed to respond on PD1/PDL1 checkpoint inhibitor treatments, the current standard of care. About 30% of NSCLC patients don't respond to checkpoint

inhibitors and this patient population lacks approved treatment options. Tedopi is also currently being explored in a phase II trial in pancreatic cancer.

Caris Life Sciences develops AI-powered predictor of chemotherapy sensitivity in MCC

Caris Life Sciences launched MI FOLFOX-ai, an artificial intelligence-based predictor of response to FOLFOX chemotherapy in metastatic colorectal cancer that demonstrated approximately 50% improvement in overall survival across two independent validation studies.

The AI-powered predictor is using Caris Molecular Intelligence tumor profiling results, and is intended to gauge a patient's likelihood of benefit from FOLFOX as a first-line regimen in combination with bevacizumab.

MI FOLFOXai was validated using two independent data sets to compare the increased benefit arm to the decreased benefit arm. The first study was a blinded, prospective analysis from retrospectively tested samples from the randomized phase III TRIBE2 study. This study showed a median overall survival improvement of 6.9 months. The second study involved several hundred cases with real-world evidence that showed a median overall survival increase of 11.8 months.

MI FOLFOXai was developed using a subset of results from the company's proprietary Caris Molecular Intelligence platform, which includes next generation sequencing for DNA mutations, copy number alterations, insertions/deletions; whole transcriptome sequencing for RNA fusions and variant transcripts; and protein testing via immunochemistry. Machine learning

algorithms were then used to create a molecular signature that was validated using the two independent data sets to compare the increased benefit arm to the decreased benefit arm.

DRUGS & TARGETS



FDA approves Imfinzi for ES-SCLC

FDA March 27 approved Imfinzi (durvalumab) in combination with etoposide and either carboplatin or cisplatin as first-line treatment of patients with extensive-stage small cell lung cancer.

AstraZeneca sponsors Imfinzi.

Efficacy of this combination in patients with previously untreated ES-SCLC was investigated in CASPIAN, a randomized, multicenter, active-controlled, open-label, trial (NCT03043872). The evaluation was based on the comparison of patients randomized to Imfinzi plus chemotherapy vs. chemotherapy alone. The major efficacy outcome measure was overall survival. Additional efficacy outcome measures were investigator-assessed progression-free survival and objective response rate, per RECIST v1.1.

Median OS was 13.0 months (95% CI: 11.5, 14.8) in the Imfinzi plus chemotherapy arm compared with 10.3 months (95% CI: 9.3, 11.2) in the chemotherapy alone arm (hazard ratio 0.73; 95% CI: 0.59, 0.91; $p=0.0047$).

Investigator-assessed PFS (96% of total planned events) showed a HR of 0.78 (95% CI: 0.65, 0.94), with median PFS of 5.1 months (95% CI: 4.7, 6.2) in the Imfinzi plus chemotherapy arm and 5.4 months (95% CI: 4.8, 6.2) in the chemotherapy alone arm. The investigator-assessed confirmed ORR was 68% (95% CI: 62%, 73%) in the Imfinzi plus chemotherapy arm and 58% (95% CI: 52%, 63%) in the chemotherapy alone arm.

EMA grants positive opinion to Adcetris combination in lymphoma indication

The European Medicines Agency's Committee for Medicinal Products for Human Use granted a positive opinion for the extension of the marketing authorization of Adcetris (brentuximab vedotin) and recommended its approval in combination with CHP (cyclophosphamide, doxorubicin, prednisone) as a treatment for adult patients with previously untreated systemic anaplastic large cell lymphoma.

Takeda Pharmaceutical Company Ltd. sponsors Adcetris.

The positive CHMP opinion is based on the results of the phase III ECHELON-2 study evaluating Adcetris in combination with CHP to a standard care, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), in previously untreated patients with CD30+ peripheral T-cell lymphoma, including the subtype

sALCL. Adcetris is an antibody-drug conjugate directed at CD30, which is expressed on the surface of several types of PTCL, including sALCL.

"There have been no significant treatment advancements for PTCL over the last few decades. Historically there have been a lack of randomized clinical studies in this setting, making it a challenge to establish an optimal therapy for these patients," Eva Domingo-Domech, Institut Català d'Oncologia – Hospitalet, Hospital Duran i Reynals, said in a statement. "Outcomes with currently available therapies are often poor, and there is an urgent need for new treatment options. If approved for adult patients with previously untreated sALCL, ADCETRIS may offer an important option for European patients."

"ECHELON-2 showed that Adcetris plus CHP demonstrated a significant improvement in progression-free survival and overall survival while maintaining a safety profile comparable to the standard of care of CHOP," Christopher Arndt, head of the Oncology Therapeutic Area Unit at Takeda, said in a statement.

The opinion for Adcetris will now be reviewed by the European Commission for Commission Decision. Adcetris is not approved as a therapy for frontline sALCL in Europe.

The ECHELON-2 study met its primary endpoint with Adcetris plus CHP demonstrating a statistically significant improvement in progression-free survival as assessed by an Independent Review Committee (hazard ratio [HR]=0.71; p -value=0.0110), 29% improvement in PFS. The safety profile of Adcetris plus CHP in the ECHELON-2 trial was comparable to CHOP and consistent with the established safety profile of Adcetris in combination with chemotherapy.

NCI TRIALS



NCI Trials for April 2020

The National Cancer Institute Cancer Therapy Evaluation Program approved the following clinical research studies last month.

For further information, contact the principal investigator listed.

Phase I - 10329

Phase I Sequential Trial of Agents Against DNA Repair (STAR)

University of Texas MD Anderson Cancer Center LAO
Yap, Timothy Anthony
(713) 563-1784

Phase I - PBTC-056

A Phase I Study of the ADAM-10 Inhibitor, INCB7839 in Children with Recurrent/Progressive High-Grade Gliomas to Target Microenvironmental Neuroigin-3

Pediatric Brain Tumor Consortium
Monje, Michelle
(650) 736-0885

Phase I/II - 10221

A Phase I/II Biomarker Driven Combination Trial of Copanlisib and Immune Checkpoint Inhibitors in Patients with Advanced Solid Tumors

University of Texas MD Anderson Cancer Center LAO
Yap, Timothy Anthony
(713) 563-1784

Phase II - 10264

The PRIME Trial: PARP Inhibition in IDH Mutant Effectiveness Trial. A Phase II Study of Olaparib in Isocitrate Dehydrogenase (IDH) Mutant Relapsed/Refractory Acute Myeloid Leukemia and Myelodysplastic Syndrome

Yale University Cancer Center LAO
Prebet, Thomas
(203) 737-7103

Phase II - ADVL18P1

An Open-Label Feasibility Study to Assess the Safety and Pharmacokinetics of Enasidenib in Pediatric Patients with Relapsed/Refractory Acute Myeloid

Leukemia (R/R-AML) with an Isocitrate Dehydrogenase-2 (IDH2) Mutation

Children's Oncology Group
Zarnegar-Lumley, Sara
(615) 936-1762

Phase II - APEC1621K

NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) - Phase 2 Subprotocol of AG-120 (Ivosidenib) in Patients with Tumors Harboring IDH1 Mutations

Children's Oncology Group
Alva, Elizabeth Duncan
(205) 638-9285

Phase III - AAML1831

A Phase 3 Randomized Trial for Patients with De Novo AML Comparing Standard Therapy Including Gemtuzumab Ozo-gamicin (GO) to CPX-351 with GO, and the Addition of the FLT3 Inhibitor Gilteritinib for Patients with FLT3 Mutations

Children's Oncology Group
Cooper, Todd Michael
(206) 987-2106

Phase III - S1914

A Randomized Phase III Trial of Induction/Consolidation Atezolizumab (NSC #783608) + SBRT Versus SBRT Alone in High Risk, Early Stage NSCLC

SWOG
Daly, Megan Eileen
(916) 734-5428