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THE CANCER LETTER
Inside information on cancer research and drug development
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# WORKING TO END CANCER IN THE TIME OF COVID-19

Since the dawn of man: when a novel virus is introduced to the human species, the world is changed forever. Despite all of our advances—we can share information around the globe in seconds and we can fly to the moon—a never-before-seen virus can stop us all in our tracks and steal people's lives too soon.

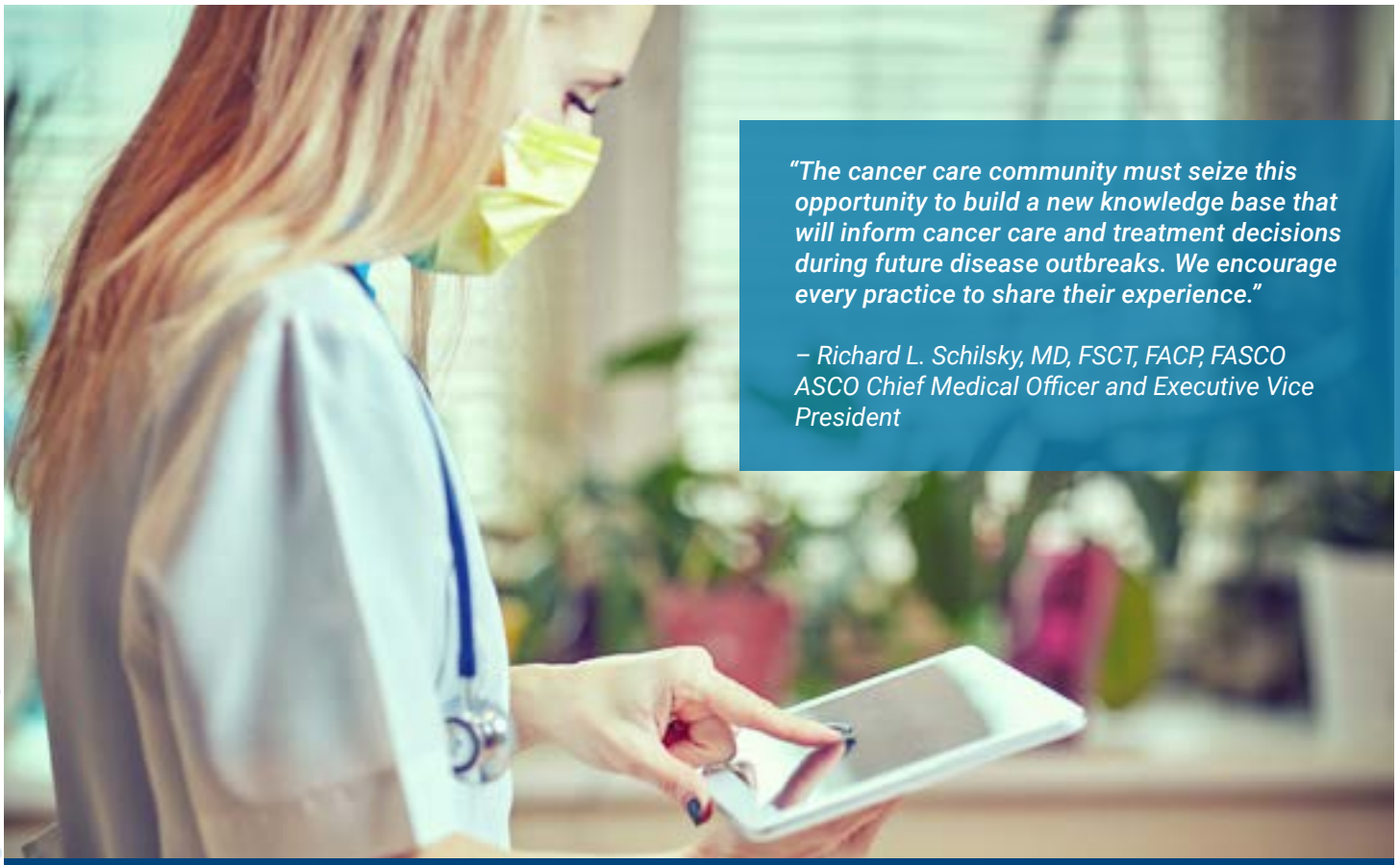
→ PAGE 5

# Help close the coronavirus data gap. Enroll in the ASCO COVID-19 Registry today.

To address the coronavirus data gap, ASCO established the ***American Society of Clinical Oncology Survey on COVID-19 in Oncology Registry***. The ASCO Registry will help the cancer community learn more about the treatment and outcomes of cancer patients with COVID-19, and how COVID-19 is impacting the delivery of cancer care.

**ASCO COVID-19 Registry Highlights:**

- Collects baseline and follow-up data on COVID-19 impact
- Delivers periodic reports with key findings
- Provides insight to inform treatment now and in the future
- Qualifies as an accepted clinical trial registry for improvement activities under the Merit-Based Incentive Payment System (MIPS)



*"The cancer care community must seize this opportunity to build a new knowledge base that will inform cancer care and treatment decisions during future disease outbreaks. We encourage every practice to share their experience."*

*– Richard L. Schilsky, MD, FSCT, FACP, FASCO*
*ASCO Chief Medical Officer and Executive Vice President*

**SIGN UP TODAY: asco.org/asco-coronavirus-information/coronavirus-registry.**

ASCO® Registry

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GUEST EDITORIAL

# WORKING TO END CANCER IN THE TIME OF COVID-19

Since the dawn of man: when a novel virus is introduced to the human species, the world is changed forever. Despite all of our advances—we can share information around the globe in seconds and we can fly to the moon—a never-before-seen virus can stop us all in our tracks and steal people's lives too soon.

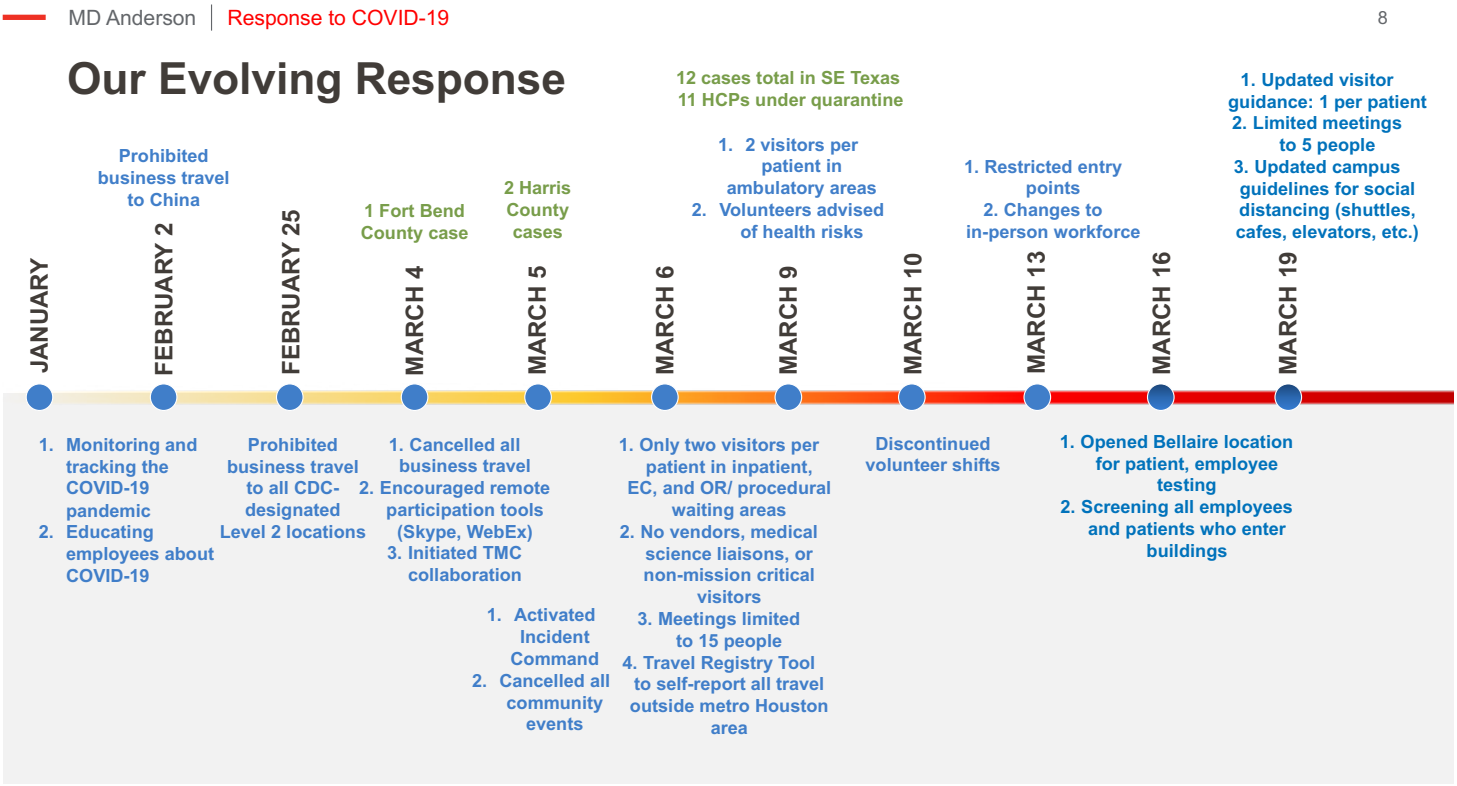
**By Peter WT Pisters, MD**
*President, The University of Texas MD Anderson Cancer Center*

At The University of Texas MD Anderson Cancer Center, we began closely monitoring and tracking the activity of the SARS-CoV-2 virus as the virus and the news started to spread in early January.

It quickly became clear that the potential for a global pandemic was real. We knew we needed to be prepared, and we started informing our employees about the virus, ordering PPE, and formulating a crisis management plan, to have it ready by late January. It was helpful to have an enterprise risk management team and a program in place that gave us a strong foundation in dynamic risk calibration, modeling and management.

MD Anderson has one of the largest and densest concentrations of immunocompromised patients in the world. We consider it our responsibility to protect the health and safety of all of our patients at all times, including during a global pandemic. As we started seeing data coming from impacted countries that showed that cancer patients who contracted the SARS-CoV-2 virus are at increased risk for hospitalization and death from the infection, we knew the months ahead would require swift, significant action to ensure we could fulfill our commitment to patients.

To guide our path forward during what we knew would become a global pandemic, we established three goals to inform all decisions: protect our uniquely vulnerable patient population, ensure the health of our workforce, and




minimize disease impact on our local community.

It is important to highlight that from the start of this pandemic, we made thousands of decisions—all with a focus on protecting our patients and employees. Many were good, some were great, and others we would not do again, but—most importantly—we have learned so much along the way, and our organization has become stronger as a result.

As a leader, I also have been tested, I have grown, and I have learned many lessons over recent months. Multi-channel communication has been fundamental to our efforts. We have prioritized daily, fact-based, transparent communication with our workforce, sharing guidance on the decisions being made and resources available.

Some of our communications tools have included: daily COVID-19 briefings each morning, often with as many as 600 employee leaders joining the 30-minute WebEx for updates; daily emails from me, with further updates; nearly 30 short videos from me distributed regularly; a comprehensive employee COVID-19 app; and virtual livestreams and town halls that have brought as many as 16,000 employees together for the live, 60-90-minute meetings. These efforts were vital, because while communication is an important part of leadership at all times, communication is essential during a crisis.

Collaboration also has been key to our response. We have partnered with other Texas Medical Center (TMC) health systems to closely work together on issues including communications and supply chain, to share information, and to help inform the public—via media and social media—about the realities of this virus.

We have worked with elected city and state officials to keep them informed—especially when difficult decisions needed to be made. We also remain connected with national groups and our peer institutions across the nation to share data and to learn from one another.

This has been a time for great partnership as we tackle this global challenge together.

## MD Anderson's clinical response

Starting in early March, we moved to scale down our enterprise in response to federal and state guidelines.

The speed at which some actions had to be taken felt as though a series of light switches were turned off. It was not easy or without pain, but the dedication and commitment of MD Anderson's faculty and staff was extraordinary.

Our effort has involved a focus on short-term immediate crisis response along with assessing long-term business con-

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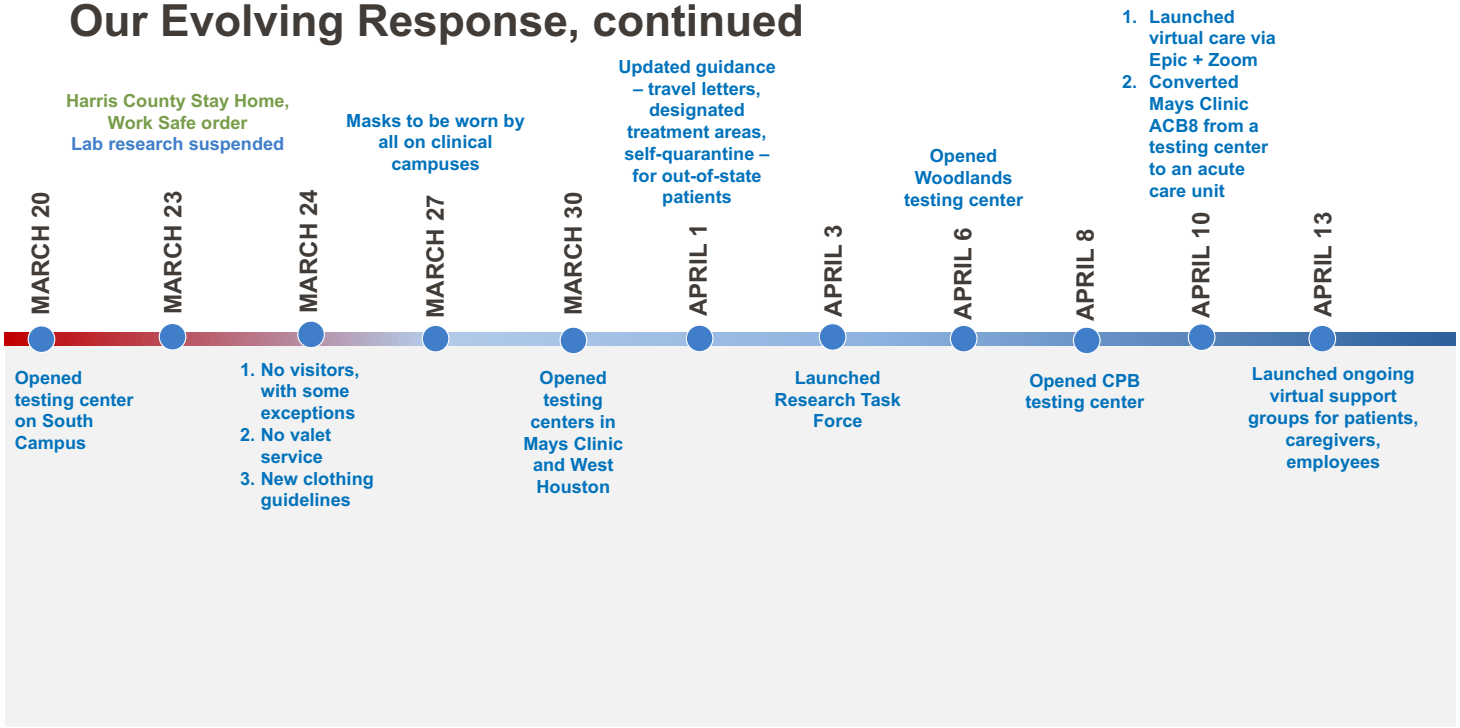
## Our Evolving Response, continued

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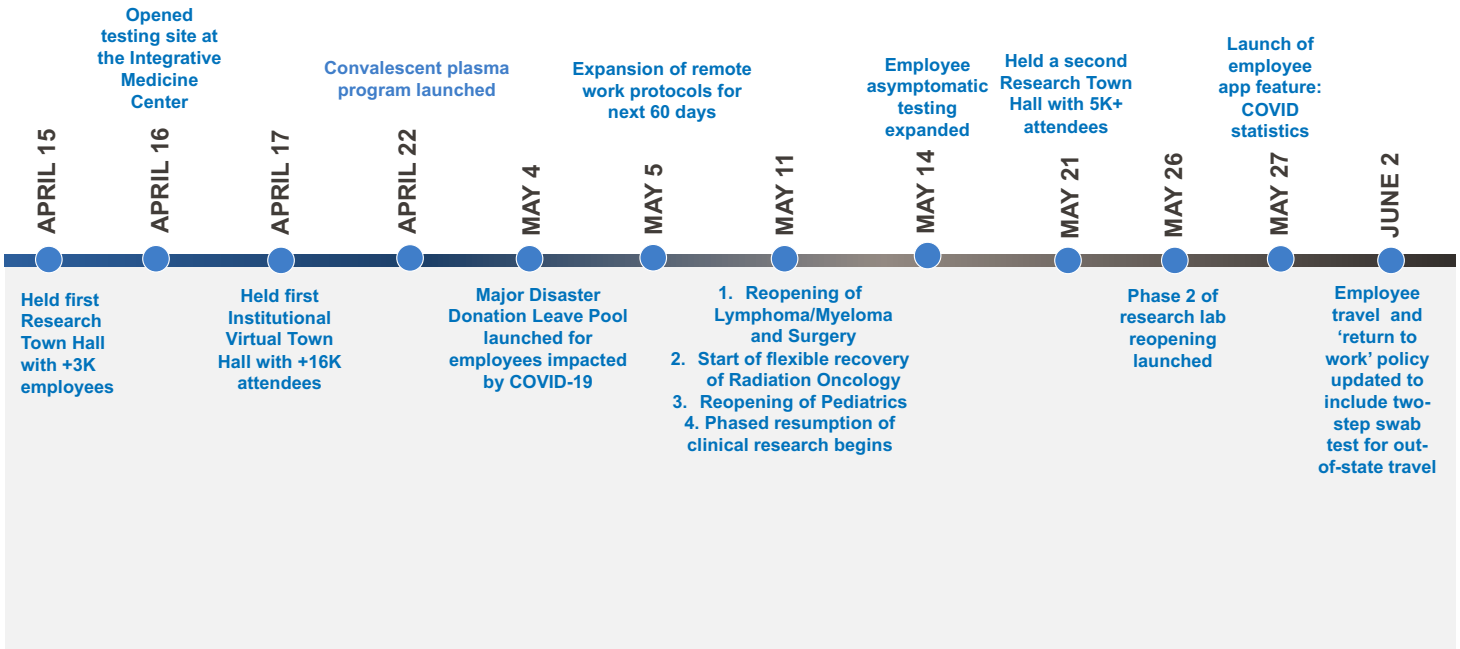
## Our Evolving Response, continued



tinuity needs. With these time frames in mind, we created a COVID-19 Core Leadership Team to act on immediate priorities and an Enterprise Resiliency Executive Oversight Committee to consider medium-to-long-term risks and opportunities.

Decisions made in those forums are reviewed by the President's Advisory Council, allowing leaders from all segments of our institution to provide perspectives and to help support sense-making in their work areas. All of these groups provide guidance and insight to inform my decision-making process.

It is important to highlight that these committees include division heads, department chairs, faculty senate members, executive leaders, and faculty and employee representatives, providing diversity of opinions from across our institution. Meetings have been frequent, discussions have been thorough and decisions are made with great thought, always keeping our three goals in mind.

Since January, thousands of decisions have been made. A sampling of those decisions includes:

- As early as in February, we started cancelling business travel and, as virus activity progressed, we asked staff to log personal travel in a central registry. At one point, all personal travel outside the state of Texas required a mandatory 14-day quarantine upon return.
- We created a perimeter around our clinical care areas to limit access points, and we coordinated symptom screening, temperature checks and masking for all.
- We reduced onsite employees at our TMC campus from a typical day of 16,500 people to, on average, only 6,500 people.

- We expanded PPE protocols to ensure everyone was safe and protected. PPE supply chain and donations allowed us to go above CDC standards throughout our experience thus far.
- We implemented a zero-visitor policy with few exceptions, and we required social distancing measures on campus.
- We launched our virtual care platform to continue serving patients unable to travel, and we tapped into MD Anderson's national network of hospitals to offer some patients care close to home.

We knew the importance of testing and moved early to stand up our own capabilities. We offer these services broadly to MD Anderson patients and employees at locations across Houston. We have the capability to conduct 1,200 tests per day, providing results within 36 hours; most are available within 24 hours.

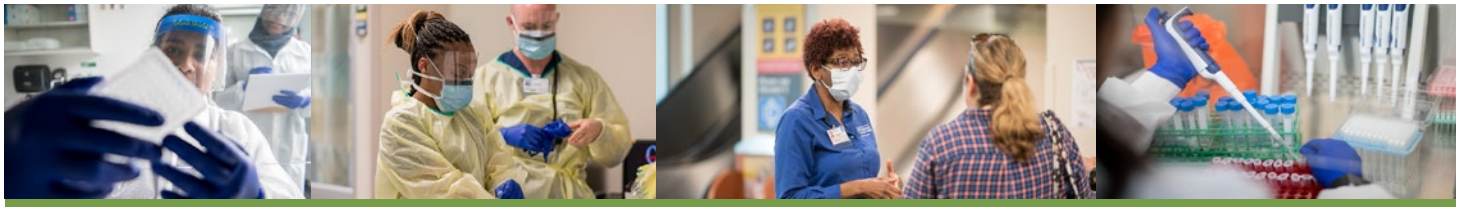
To provide added assistance to those in our community and across Texas, we also conduct testing for county hospitals in the Harris Health System and for the Texas Department of Emergency Management.

As of June 9, we have tested nearly 8,000 MD Anderson patients. Of those, 103 patients have tested positive for COVID-19 and 38 have been treated in our inpatient hospital. Sadly, four patients have died, making our mortality rate significantly lower than published data from other countries.

More than 2,200 employees have been tested; 126 have been COVID+ and most already have returned to work. Among more than 22,000 employees, about .5% of our workforce have been infected. We attribute these low rates to our employees' shared commitment to proper use of PPE, social distancing, and hand hygiene—at work and at home.

We also expanded our offering to include asymptomatic testing for any employee who requests it. More than 600 employees have undergone asymptomatic testing and only four have tested positive.

We fully recognize that this crisis has both physical and emotional impact on our employees. Consequently, we have



## Protecting our patients and our employees' physical security and infection control

- Limited access points
- Reduced onsite employees: 16,500 → 6,500
- Screening and masking for all
- Expanded personal protective equipment (PPE) protocols
- Testing for all employees, regardless of job role or symptom
- Expanded testing for patients
- Moving to:
  - Scale up
  - Digitize via employee app

## COVID-19 Personal Protective Equipment (PPE) Guidelines

| MINIMUM PPE | AT-RISK: Asymptomatic patient with high-risk exposure | | | SYMPTOMATIC: Patient has symptom(s) of COVID-19, in provider's judgment | | CONFIRMED | HIGH-RISK PROCEDURES |
|---|---|---|---|---|---|---|---|
| **FOR ALL** (Includes asymptomatic patients undergoing testing in accordance with our testing criteria) | **OUTPATIENT** | **EMERGENCY CENTER** | **INPATIENT** | **OUTPATIENTS** (History portion of patient visit only) | **ALL** (Including outpatients during Examination portion of patient visit) | **ALL** | **ALL STAFF WITHIN 6 FEET OF PROCEDURE*** |
| | | | | ***For outpatients, staff performing history only need to wear:*** *face mask and gloves and maintain 6 foot distance, for less than 5 minutes* | Eye protection | Eye protection | Face shield |
| | | Gown | Gown | | Gown | Gown | Gown |
| | Gloves | Gloves | Gloves | Gloves | Gloves | Gloves | Gloves |
| Face mask | Face mask | Face mask | Face mask | Face mask | N95 | N95 | N95 |
| **Staff, visitors, and contractors** are required to wear a face mask.<br>**Ambulatory patients** are asked to wear a mask at all times on premises.<br>**EC and admitted patients** are asked to wear a mask when within 6 feet of staff. | At-Risk means patient presents with:<br>Travel outside US in the last 14 days, or a household member with COVID-19 confirmed in last 14 days<br>AND<br>has no symptoms that would justify testing, in the provider's judgment | | | Symptomatic means patient presents with any one or more of these symptoms, and provider deems that testing should be performed:<br>• Fever<br>• Respiratory symptoms (cough, SOB, sore throat)<br>• Chills<br>• New loss of smell or taste<br>• Muscle pain<br>• GI symptoms (nausea, vomiting, diarrhea)<br>• CXR or CT suspicious for COVID-19 | | Confirmed positive laboratory test results for COVID-19<br>For extended use and reuse of N95 respirators, a face mask or face shield may be worn over N95 to help prevent surface contamination. | See list of procedures designated as high risk by MD Anderson, in PPE protocols.<br>* **Those beyond 6 feet** wear face mask and eye protection but not N95. Use this strategy during intubation/extubation, for example. |

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

**Cloth face coverings, recommended for use in the community, should not be worn at MD Anderson.**
For full details on proper PPE, review the PPE protocols.

## Our Core Value of Caring remains steadfast…

- **60K+ employee** leave hours donated
- **$170K+** raised in MD Anderson's Caring fund
- **100+** daily team shout outs in morning briefings
- Messages of encouragement for patients and frontline heroes
- Patient celebrations
- Weekly employee support group sessions
- Invaluable patient and caregiver support
- PPE and other in-kind donations
- Employee choir performance that went viral online and in the media
  - Watch it at https://bit.ly/37IJI25


increased our focus on ensuring the safety, the security and the physical and emotional well-being of our workforce.

To understand employees' concerns at scale and over time, we conduct pulse surveys on a frequent basis. With regard to employee worry and anxiety, we want our workforce to be able to tangibly grasp that we understand how stressful this period in time is for them and for their families.

Our second employee pulse survey garnered responses from 71% of our employees from all areas of the institution. More than 88% of participants believe their health and well-being is a top priority for MD Anderson; 86% feel supported by their managers in making decisions about health and well-being; and nearly 95% believe MD Anderson is doing what is necessary to support our patients during the pandemic.

The results of these surveys help inform our continued efforts to support our employees' needs and to enable us to target resources and attention to specific units that may need more support.

Importantly, we also offer counseling and access to financial support through our Caring Fund, an employee assistance fund that allocates grants to co-workers who are experiencing undue hardships as a result of the virus.

Anyone can contribute to the fund via online donations, and MD Anderson employees can elect for payroll deduction. We have funded disaster leave for employees unable to work their full hours to maintain their health insurance and full benefits.

We also created an opportunity for employees to donate vacation and extended illness benefit hours for others to use, and the response has been unbelievable: 60,000+ hours have been donated, to date.

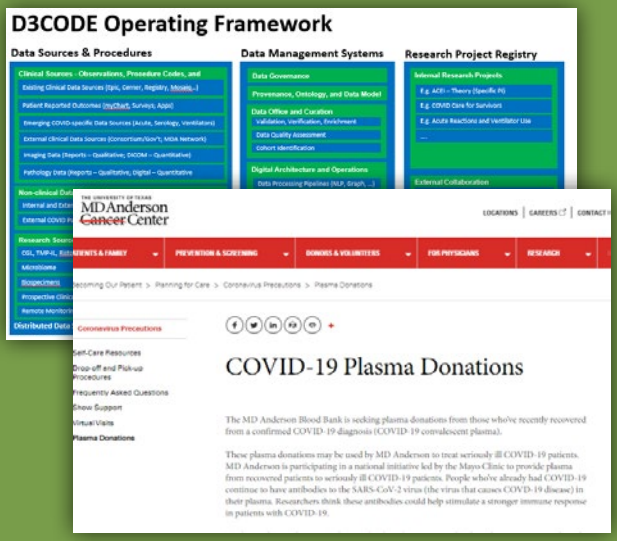
## Research response was difficult, but necessary

At the end of March, as daily case volumes in the Houston region jumped, and trajectories showed Houston tracking with and at times ahead of Wuhan and Lombardy, basic and clinical research efforts were modified or suspended in order to protect our patients and employees.

With the pandemic accelerating, a difficult decision was made by our Chief Scientific Officer Dr. Giulio Draetta to require researchers to safely decommission ongoing experiments, store reagents in the appropriate manner, and power down instruments for an unknown length of time. Valuable research tools, including animal models, cell lines and reagents, were preserved as much as possible to enable continued research when laboratory activities resumed.

## Key COVID-19 research efforts

- **Interdisciplinary collaboration**
  - 2 proposals for National Cancer Institute's call for COVID-19 research
- **Multidisciplinary collaboration between data science and research**
  - Data-Driven Determinants for COVID-19 Oncology Discovery Effort (D3CODE)
- **National collaboration with Mayo Clinic**
  - MD Anderson's participation in convalescent plasma initiative




Impressively, during an extremely difficult time for our researchers, they collected critical reagents and PPE supplies found in their laboratories and donated them to support our clinical teams. We take great pride in these acts of collaboration and commitment to the greater good of our institution and to our patients.

Where possible, researchers have worked remotely, and outstanding science has been generated during this time, including work focused on COVID-19 and efforts focused on grant-writing and fostering future collaborations. In response to the numerous ideas and proposals put forth for meaningful research focused on the virus and associated disease, we established the COVID-19 Research Task Force.

Through the guidance of several focused workgroups, the task force is responsible for prioritizing and advancing COVID-19 research projects. Already, two MD Anderson research projects were chosen by the National Cancer Institute to advance for full proposals. We also are collecting plasma donations from those who have recovered from COVID-19, and we are participating in a national initiative to provide that plasma to seriously ill COVID-19 patients.

We also established our Data-Driven Determinants for COVID-19 Oncology Discovery Effort (D3CODE), which created a cross-functional, institution-wide data science initiative linked to the pandemic. Under IRB approval, we activated a protocol to facilitate data-focused research related to COVID.

This eliminated the need to submit individual protocols solely for the purpose of aggregating and analyzing this data. The goal of this initiative is to provide investigators with a common, curated and readily available source of aggregated COVID+ patient data to empower the rapid prosecution of research questions.

Modifications also had to be made to clinical trials to ensure patients remain safe and receive the care they need, while reducing in-person interactions to only those that are essential for the provision of safe medical care.

Throughout the pandemic, many of our clinical trials continued using remote monitoring and virtual care. Clinical trials that could not continue using remote methods of interaction were temporarily suspended.

## Education continues, with modifications, during our response

Our education mission has continued throughout our response to COVID-19. Early on, our educators worked to develop training for our patient care teams on proper PPE use and patient care best practices to safely care for COVID+ patients.

Our fellows and residents have continued to be integral parts of our care

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teams, and those who have expressed interest in caring for our COVID+ patients have been invited to participate in this learning opportunity, when possible.

Our School of Health Professions (SHP) has continued courses online and is hosting virtual open houses for prospective students. Many of our students have supported important efforts during the pandemic. A great example is that current SHP Molecular Genetic Technology students assisted with our routine diagnostic testing while our Molecular Diagnostic Lab employees focused on developing and processing COVID-19 tests.

At our Graduate School of Biomedical Sciences, students have been successfully defending their theses over web conferences in preparation for graduation. Many of our summer research programs also are creating virtual experiences to engage high school, college, graduate students and postdoctoral fellows in science and research lectures, career advice and more.

Our commitment to educating future cancer health care providers remains strong, and we are working to safely support their learning during this unprecedented event that may shape many of their careers moving forward.

## Prevention services scaled back

Although clinical screening and prevention services were scaled back during the pandemic based on federal and regional guidance, we recognize the importance of quickly bringing these services back online for our patients, and we are working to do so in locations all over Houston.

This will be enhanced by ensuring we can ease the anxieties that healthy people have about accessing hospitals—fearing the risks of contracting COVID-19 at a health care facility to be far greater than at the grocery store or other public venues where the sick do not congregate.

Throughout the pandemic, social media has played an important role in continuing to communicate prevention messages. Those stories and tips have served as a reminder that there always are steps that can be taken to reduce cancer risk.

## Recovery creates opportunities

If our initial response was like turning off a light switch, our recovery is like using a series of dimmer switches with the ability to adjust up and down based on COVID-19 case volumes in the area.

The principles of our recovery are that it be strategic, stepwise, fact-based and data-driven. It is clear that COVID-19 will be with us for years, and we must move forward understanding and accepting this new reality. It is essential that we continue our commitment to cancer patients and clinical trials while fully integrating protection for our patients and our employees in our recovery plan.

We know that we cannot just open the doors. We have to create social distancing capacity and redesign clinics, and we even have to rethink long-term changes to how individuals enter the institution. We also must maintain a disciplined way to preserve at least 15% of our beds, as required by our state's governor, for the second surge of COVID-19, which may be upon us now.

The goal that we initially set for full reopening to normal operating volumes was Nov. 1. Already, we are far outpacing our goal. We are learning from our experience and transforming operations and medical practice, moving forward in dramatic ways that extract elements from our draft strategic plan and allow for accelerated implementation.

So, what has changed, and how are we making such swift progress?

We first looked at what has been impacted by the decrease in patient volumes. We rescheduled appointments and got our surgical services back to full capacity. We also found that we can make improvements to our surgi-


cal scheduling, which is making a positive impact.

We have focused initially on service lines that offer high-impact clinical trials, including Lymphoma and Myeloma with our CAR T and CAR NK trials. We also have explored ways to improve our patient navigation process.

Regulatory changes have allowed for increased virtual care and transformation. Virtual care is one example of an initiative that was included in our draft strategic plan. Traditionally, getting an effort like that implemented would take three years, whereas in a crisis we made it happen in three weeks. Already, virtual care has proven impactful for patients and providers, with nearly 20,000 appointments having been completed using our platform.

We have increased the frequency of working with our patients to establish and document goals of care based on each individuals' preferences and beliefs. This ensures that there is complete alignment and mutual understanding of the fundamental aspects of the pace of disease, changes in prognosis, and patient and family goals of care. While we always strive for a cure, compassionate care aligned with the patient's goals is of greatest importance.

We also are developing plans to continue allowing a portion of our employees to work remotely—even after the current concerns have been alleviated. This concept would have been unheard of just a few months ago, but now we are aiming for a substantial proportion of our workforce to be remote for increased efficiency, effectiveness, work-family balance and a reduced carbon footprint.

We also know that our workforce has more than 6,000 children under the age of 14 whose needs must be factored into our planning if onsite school classes are not offered in the fall.

In our research areas, our timely recovery is critical as we know clinical trials often are a patient's best treatment option and that resuming activity maintains grants and other external funding sources.

Additionally, we want to get our researchers back to work as that has a positive impact on their projects, on their career growth opportunities and their well-being.

Our research recovery is happening in phases: first, preparing and getting buildings back online; second, returning to work in shifts to enable extra safety precautions; third, full capacity and functioning within the "new normal," and last, at some undetermined date in the future, business as usual allowing for in-person seminar series and business travel.

We currently are in the second phase of our recovery, with great momentum carrying us forward. We recognize that the pace of our phases must be dovetailed with the evolution of the secondary peaks in the pandemic and the development of a safe and effective vaccine(s).

We are cognizant of the reality that it is not the date of the availability of a vaccine that is a pivot point, but that it is the date that 100% of our workforce has developed antibodies through SARS-CoV-2 or via vaccination.

## Overcoming financial hurdles

Like most hospitals around the country that have been impacted by COVID-19, MD Anderson is projecting a financial loss in fiscal year 2020.

Currently, we are well positioned to overcome these financial challenges based on prudent decision-making and the institution's overall financial strength at the start of the pandemic.

That said, we have taken additional steps to respond to financial results and to ensure the long-term health of the institution. Some of those steps have included the implementation of a hiring freeze until the end of the fiscal year (Aug. 31, 2020), elimination of incentives, the reduction or elimination of overtime, the reduction of contrac-

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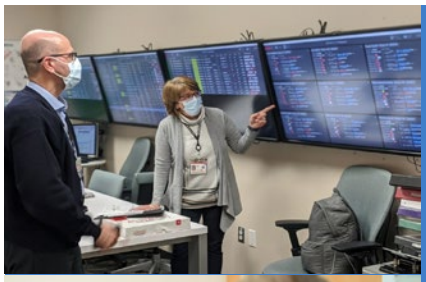
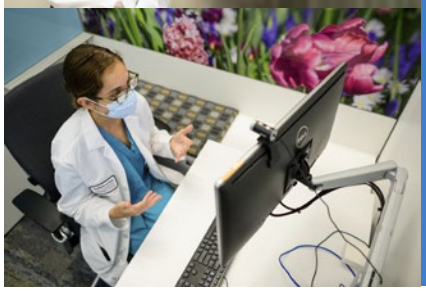




## The silver lining : An acceleration of our strategic plan concepts

- Innovative approaches to medical practice
  - Improved scheduling
  - Virtual care
  - Goals of care
- Operational changes to improve access during recovery effort
- Adaptation to working remotely, where possible
- Enhanced focus on team-science and multidisciplinary research collaboration

tor and consulting agreements and the deferment of some facility and IT projects. Business travel also remains on hold due to the virus.

Our team effort has helped minimize the financial loss for the institution, and, as one of the largest employers in Houston, it has ensured our ability to remain firmly committed to job security for our workforce. We strongly believe that we have a responsibility to protect our employees and their families during a national recession and economic headwinds in Texas related to energy markets and crude oil prices.

## Coming together to emerge stronger, safer and better

Our collective focus has been on our three goals of protecting our patients, ensuring the safety of our employees and minimizing the impact on our community.

By working to accomplish our goals, we have been able to ensure the safety of our patients and our people while continuing our important work to end cancer. We recognize the formidable role we play in advancing cancer discoveries through research, in educating and training future health care providers and in preventing cancer before it starts through screening efforts and early detection.

While much has changed, we never have lost focus on our mission. We have come closer together as an institution, we have learned so much, and we remain committed to a safe and complete recovery.

There is no doubt that this has been a very difficult time for everyone involved—patients, their loved ones, health care providers, researchers, and our entire community. We are committed to seeing those patients who need safe cancer care, to accelerating discovery through our research efforts and to ensuring availability of cutting-edge clinical trial options for our patients.

We stand with our researchers and are committed to ensuring they have the support they need to continue doing groundbreaking work. We stand with our physicians, our advanced practice providers, our nurses, our patient transporters, our entry screeners and all of our employees on the frontlines of this crisis.

And we stand with all of you—our peers in the cancer community. We have an important role to play in ensuring the health of our nation and in caring for cancer patients, many of whom will need us now more than ever. I applaud all of you for the work you have done during COVID-19.

And as I tell my team of 22,000 cancer fighters: Together, we will emerge stronger, safer and better, forever.

# #WhiteCoats4BlackLives aims to lead to real change in oncology

## "I've never been more hopeful in my entire life"

*By Alexandria Carolan*

A movement that began with a fatal chokehold on a Minneapolis street grew into demands for police reform, but outrage didn't stop there. Amplifying, reverberating, it became a call for racial justice in medicine, in oncology.


The #WhiteCoatsforBlackLives march in Washington, D.C. June 6
*Photo courtesy of Pock Utiskul*

The COVID-19 pandemic focused America's attention on health disparities. The murder of George Floyd led them into the streets, and they kept going, people from all walks of life, including thousands of doctors young and old, out there, taking aim at racism in medicine.

"White Coats for Black Lives extends much further than the knowledge of the violence, a knowledge of the killing of young men and women by police, a knowledge of the police brutality against blacks. Consequently, all of this affects health care," Edith P. Mitchell, a member of the President's Cancer Panel, clinical professor of medicine and medical oncology in the Department of Medical Oncology, director of the Center to Eliminate Cancer Disparities, and associate director of Diversity Affairs at Sidney Kimmel Cancer Center at Jefferson, said to *The Cancer Letter.*

Some say this is the turning point, that clear changes will be made to increase diversity in leadership positions, that work will get done to narrow health disparities, that black patients will get the same care as white patients.

"I am more than cautiously optimistic that this is our first step to healing, that this is our first step to really getting real change," Robert Winn, director of Virginia Commonwealth University Massey Cancer Center, said to *The Cancer Letter.* "I've never been more hopeful in my entire life. I think people are waking up from their slumber, and as a country, we are embracing and becoming our best selves."

There are no shortcuts.

"I'm thrilled that doctors are concerned about health disparities, but we need to get at the social root of the cause. And we need to tackle all aspects of the health disparities problem—including, why is it that American society has created this 'thing?'" Otis Brawley, Bloomberg Distinguished Professor of Oncology and Epidemiology at Johns Hopkins University, said to *The Cancer Letter.*

## Something is different

Perhaps the reason this movement feels so different, is the words "Black Lives Matter" have permeated the mainstream.

> "I've never been more hopeful in my entire life. I think people are waking up from their slumber, and as a country, we are embracing and becoming our best selves."
>
> *– Robert Winn*

"I would say, even as recently as a few months ago, to talk about police brutality—to even say the words 'Black Lives Matter' was something that was felt to be political or controversial," Malika Siker, associate dean of student inclusion and diversity in the Office of Academic Affairs, associate professor in the Department of Radiation Oncology, student pillar faculty member, at the Robert D. and Patricia E. Kern Institute for the Transformation of Medical Education, said to *The Cancer Letter.*

"I feel like that conversation has changed now, and people are no longer afraid to say those words, and not just say the words, but understand what they mean—and show a commitment to social justice and anti-racism," said Siker, who is also academic vice chair of the Community Advisory Board at MCW Cancer Center, Medical College of Wisconsin.

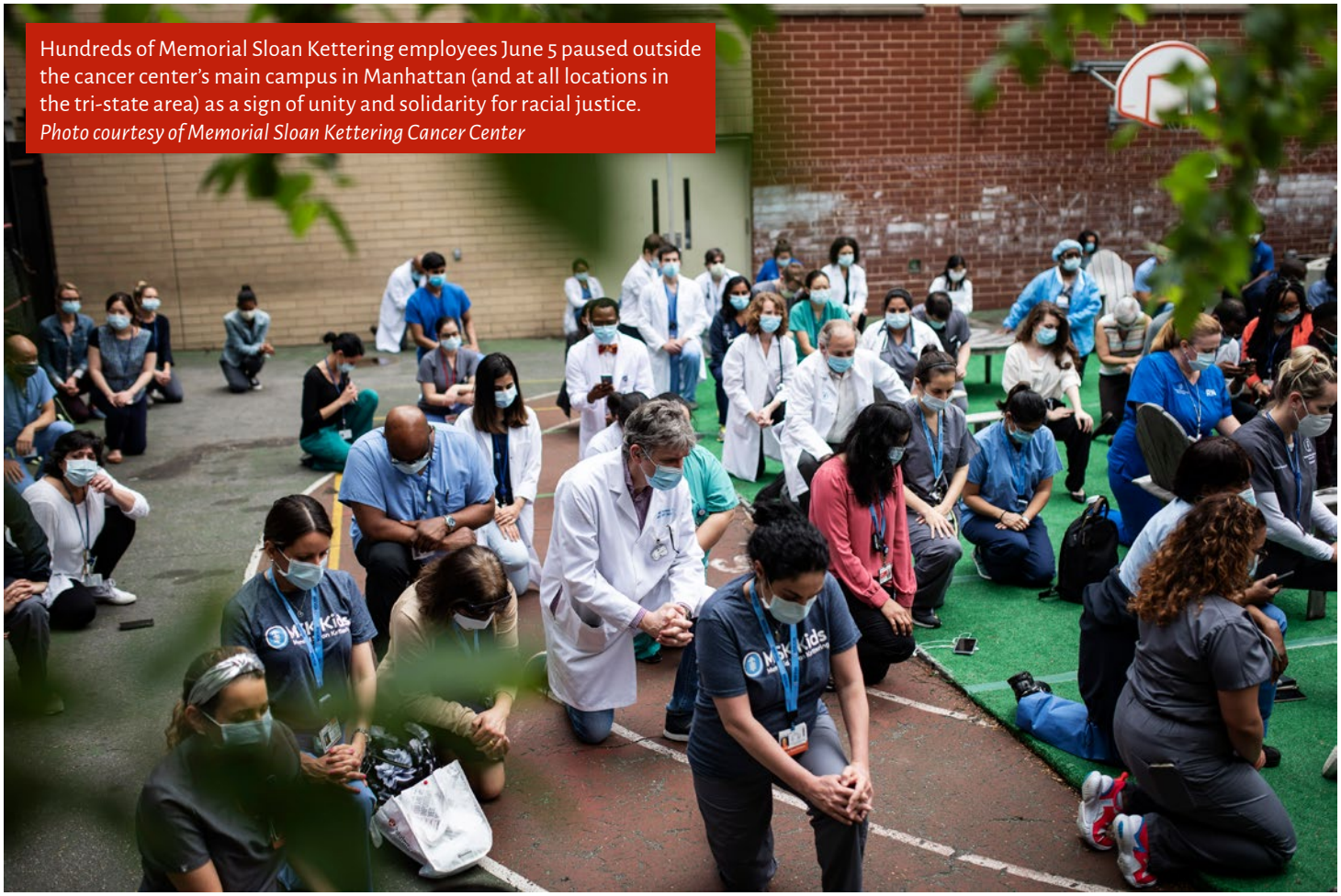
In oncology, these doctors say staying silent about racism is no longer an option. If a physician's goal is to alleviate human suffering, how can the quest for racial justice be overlooked?

"If you don't step out, there is no middle ground. We've got to be anti-racist, and every person in their position, in the medical field, needs to speak out, step out and do what we need to do so that we are removing the knee from the neck in all areas," Mitchell, a former president the National Medical Association, said. "We can therefore face a world of equity, health care equity, for all. It's not only ethically the right thing to do, but for this country—for health care, for all, it's the best instance."

At the start of Mitchell's career, in the year 1972, she recalls being fitted for her white coat as a sophomore. The seamstress asked: "Are you going to like working in the kitchen at the hospital?"

Physicians "have a responsibility to address racism," Christina Chapman, assistant professor in the Department of Radiation Oncology, University of Michigan School of Medicine, and Center for Clinical Management Research, VA Ann Arbor Healthcare System, said to *The Cancer Letter.*

"It's also the recognition that the physician does take a white coat off at the end of the day, but still has that responsibility, even in other sectors of their lives, to take a stand on racism, as one of the very critical roles in the healthcare system," Chapman said. "It's to unite, and to not give physicians a pass on their responsibility in addressing racism."



Hundreds of Memorial Sloan Kettering employees June 5 paused outside the cancer center's main campus in Manhattan (and at all locations in the tri-state area) as a sign of unity and solidarity for racial justice.
*Photo courtesy of Memorial Sloan Kettering Cancer Center*


Johns Hopkins faculty and staff take the knee in solidarity
*Photo courtesy of Lawrence Brown, Johns Hopkins Medicine*

Until recent events, doctors whose work isn't focused on disparities could simply not think about injustice. If they didn't live it, or actively engage with it, they didn't have to talk about it.

"On the end of health disparities and our day-to-day lives as oncologists, it's easy to just sort of ignore, or be very casual about the health disparities that we see and we encounter," Curtiland Deville, associate professor of radiation oncology and molecular radiation sciences at Johns Hopkins University School of Medicine, said to *The Cancer Letter.*

"I hope that this time it helps people take it to the next level—really trying to solve the cancer disparities that they see in the communities they serve, or even just at the individual level of the patient, or the immediate patient that they have," Deville, who is also clinical director of JH Sibley Radiation Oncology, and co-director, of JH Sibley Prostate Cancer Multidisciplinary Clinic at The Kimmel Cancer Center Sibley Memorial Hospital, said.

## Protesting in the era of COVID

The decision to come out into the public square is never trivial.

Police have tear gas, a chemical weapon, no less. They have rubber bullets, which hurt like hell and can put your eye out. They have pepper spray, which adds injury to humiliation. They slug you with their truncheons, knock you to the ground, bind your hands with a zip tie behind your back, cart you off, and maybe tell your employer, whose views on racial justice might differ from yours.

The risk of COVID-19 makes the threat bigger.

"If you need to protest, there is something that is a threat to your safety and your security and your livelihood—and you have deemed that that threat is greater than the immediate threat of the coronavirus," Deville said.

> "We've got to be anti-racist, and every person in their position, in the medical field, needs to speak out, step out and do what we need to do so that we are removing the knee from the neck in all areas."
>
> *– Edith P. Mitchell*

If you've been schooled in public health issues, you might find it hard to argue that racism is anything other than a public health issue. You would also see the overlap of COVID-19 and police brutality. George Floyd survived the former, but was killed by the latter.

"There are two pandemics, there are two infectious diseases. There's COVID-19, and there's racism. Racism hasn't gone anywhere, and racism is of paramount importance," Chapman said.

"The impact of racism extends beyond just the risk of police brutality and murder—people aren't simply out there protesting because of what happened to George Floyd. They're protesting because they know that the system that allowed that police officer to do what he did is the same system that creates residential segregation, and poverty, and health inequities that black people die from," she said.

On June 1, in Washington, D.C., in Lafayette Square, a park across Pennsylvania Avenue from the White House, police used tear gas, rubber bullets, flash bangs, horses, and a helicopter on peaceful protesters to make it possible for President Donald Trump to hold up a Bible, using St. John's Episcopal Church as a backdrop.

Deville marched down the same street less than one week later, on June 6. The temperature was in the 90s that day, as tens of thousands of demonstrators took to the streets to let it be known that Black Lives Matter. Protesters marched peacefully to the White House from all directions—the Lincoln Memorial, the U.S. Capitol, the National Mall. Chances are that if you were anywhere near downtown D.C. that day and you weren't already in a protest, you would have become a part of one.

By then, D.C. Mayor Muriel Bowser had ordered that two blocks of 16th Street NW leading to Lafayette Park be renamed Black Lives Matter Plaza.

The words BLACK LIVES MATTER are emblazoned in yellow on the asphalt—impossible to miss.

"It was a shift in what was becoming a very negative and hostile kind of situation, into a more positive direction forward," Deville said. "Being able to be there for an hour or two was a very positive feeling."

The chants were unforgettable:

"Say her name: Breonna Taylor. Say his name: George Floyd."

It's a call and response.

"It's not just black people, marching, it's all kinds of backgrounds who are, equally as enthusiastically shouting," Deville said. "You really do feel it that they are just upset, and agitated, and not holding back. And they're shouting—these black people that were killed—they're shouting their names out. It was very powerful."

The marches by the White Coats for Black Lives movement were held in multiple cities. Students, faculty, and staff showed up on June 5 at Johns Hopkins University campuses. Deville was there, taking a knee alongside other protesters.

Institutions participated, too. On the same day, Memorial Sloan Kettering Cancer Center, like other hospitals across the U.S., held a moment of solidarity. Hundreds of MSK employees joined in. At Chapman's University of Michigan School of Medicine, more than 1,000 students, staff, and faculty called in to a virtual protest organized by the University of Michigan Black Medical Association. Chapman was one of the virtual attendees.

The decision to protest is complicated for oncologists, who took the risk of being exposed to SARS-CoV-2.

The risk was worth it for Allison Betof Warner, assistant attending physician in the Melanoma Service and Early Drug Development Service at MSK. She stood with nearly 3,000 other health care workers in the East Meadow of Central Park.

"Living in New York City and having worked on the front lines of COVID, I am very wary of any groups of people. That being said, I think it's critical to have the voices of healthcare workers heard. Both COVID and cancer disproportionately affect people of color," Betof Warner said to *The Cancer Letter*. "Racial disparities in access to health care profoundly affect our patients."

Betof Warner wore an N95 mask. She maintained her distance from other participants, who were primarily healthcare workers in New York. Masks were distributed to anyone who didn't have one.

"I firmly believe that racial disparities are a public health issue, and therefore, it's critical that we hear from doctors, nurses, and other healthcare workers that the time for change is now," she said.

Protesting is a personal matter. Siker doesn't judge those who choose to, or who choose not to.

"At the end of the day, it comes down to an individual choice. For me, as an advocate, as somebody who's committed to social justice—and an oncologist still actively treating cancer patients—this has been a really tough decision," MCW's Siker said. "Because I know that if one of my cancer patients were to see me at an event, they might be disappointed that I would be putting myself at risk of contracting the virus, and therefore putting them at risk when they come to the clinic."

Chapman agrees. "I treat head and neck and lung cancer, and my patients tend to be not only immunocompromised—because most of my patients are receiving concurrent chemotherapy—and given that I treat lung cancer and I work at the VA, a lot of my patients have bad lung function," Chapman said. "So, for me, I decided, given the risks to my patients, I haven't gone out there."

The role of the physician is to provide guidance, to educate protesters on how to protect themselves, Deville said.

"As a physician, I think you can educate people. If you're going to go out there,

maybe there is no 100% safe way, but certainly, there are things you can do to try to minimize your risk. I mean, we tell people that all the time, right?" Deville said.

Fred Hutchinson Cancer Research Center and Seattle Cancer Care Alliance released a guidance for employees protesting in the time of COVID-19:

- Wear a mask or face covering that fully covers your nose and mouth.
- Strongly consider wearing or having ready access to goggles or eye protection for added protection (avoid wearing contacts).
- Bring hand sanitizer and use it frequently.
- Avoid sharing drinks, carrying other's signs or touching objects that others have touched.
- Attempt to limit your group size and maintain six feet of physical distance whenever possible during the activity.
- Try to avoid crowded activities that involve shouting or singing in close proximity to others, and avoid those who are not wearing masks or face coverings if possible.
- Bring your own water, food, or other personal items.

"The epidemiological principles of pandemic containment have not changed—it has always been to limit exposure, wear a mask and practice other precautions," Ishwaria Subbiah, palliative care physician and medical oncologist in the Department of Palliative, Rehabilitation and Integrative Medicine, Division of Cancer Medicine, at MD Anderson Cancer Center, said to *The Cancer Letter.*

"Assuming no legislative mandates on gatherings are in place, the decision to engage in a peaceful assembly is the individual's to make. Patients with health concerns can engage their medical team to assist through a discussion of the risks to self and others of person-to-person COVID-19 transmission," Subbiah said.

Risk-taking is subjective. A pandemic makes the downside steeper.

"If you have the luxury of having the conversation around, 'Should I weigh this versus that,' then, you know, that's a privilege in itself that you should be aware of," Deville said. "I don't know that a protest occurs for convenience. If you look throughout history, when did people protest when it was convenient?"

While Hopkins's Brawley is hopeful that this movement will spark real change, he is concerned that COVID-19 will spread as a result of these protests—and African Americans have already been the hardest hit population in the U.S. African Americans make up 13% of the U.S. population, but comprise greater than 33% of all COVID-19 deaths.

> There are two pandemics, there are two infectious diseases. There's COVID-19, and there's racism. Racism hasn't gone anywhere, and racism is of paramount importance.
>
> *– Christina Chapman*

"We keep talking about this as if it's a tidal wave. I think there's going to be a series of big waves—not one big tidal wave. I think we're going to see it in the fall, August, September," Brawley said. "I cannot say that people ought to protest and not worry about the coronavirus. Every protester needs to understand the risks that they are putting themselves in."

## Diversifying the workforce

While the oncology workforce is growing increasingly diverse, the leadership still appears to be predominantly white and male.

There are a total of 71 NCI-designated cancer centers. VCU Massey's Winn is the only black director. No data exist on self-identification by other directors. There are nine women directors (*The Cancer Letter,* June 5, 2020).

Senior leaders at cancer centers are "finally starting to really grapple with the issues around diversity within their own ranks, or the lack thereof," Winn said. "In fact, I think that it's probably been the first time in my life time that I've seen CEOs and deans and people not just reflect, but look at their own institutions and say, 'How can I be wanting to aspire to actually have diversity and not have any in my own ranks?'"

Leaders of many institutions have used the words "Black Lives Matter" in their public statements.

"People need to take a critical look at their lives, their circles of influence and power, and be intentional about wielding that power in a way that includes voices that may not be at the table," MCW's Siker said. "How that looks for each individual may be different."

Mitchell agrees. "How many deans do we see are African Americans? How many professors are at the highest ranks and are African American? How

many hospital directors, and how many cancer center directors are African-Americans?" Mitchell said.

And what about funding?

"NIH is evaluating how many individuals of African American or other underrepresented minority descent receive top grant funding from NIH. NIH is therefore contributing resources to study this and to improve the number of individuals receiving grants, and who become grantees for NIH funding," Mitchell said. "This goes farther than police brutality, it's involved with equity, and diversity, and inclusion."

For Deville, workplace diversity is a prerequisite to addressing health disparities and health equity.

"In the area—I went into prostate cancer, the reason I was drawn to it was because I was going through my rotations and saw a lot of black men with prostate cancer. The fact that their outcomes were worse—they have death rates twice as high—I was feeling like, why aren't people as wound up about this as I'm feeling?" Deville said.

"It says to me that, what a shame that patients often do not have providers that look like them. They often don't have that option in a large proportion of healthcare settings throughout the U.S. It's just sad."

## "The gravity of racism"

NCI requires that its designated cancer centers have Community Outreach and Engagement programs focused on addressing health disparities.

"Doctors are realizing that they have a social obligation. I actually wish they would push it a little further, because even amongst doctors—the thought is always the racism, getting rid of the racism when the patient has a diagnosis and is being treated," Brawley said. "And that, certainly, is an important part of it. But the thing to realize is that the police issue, the health disparities issue—they are all part of one thing. They're held together by this gravity of racism."

This gravity of racism is entrenched in an almost endless array of health inequities that affects the black cancer population. There are multiple barriers to treatment: cost, travel, inferior quality and delivery of care, and distrust.

African Americans have higher incidence of hypertension, diabetes, lung disease, prostate cancer, and now, COVID-19. To pull patients out of peril


Physicians and health care professionals standing with the #BlackLivesMatter protest in Washington, D.C. June 6
*Photo courtesy of Pock Utiskul*

requires concerted effort by leaders in health care.

"Therefore, we really must increase insurance for individuals. Again, it's been recognized that those individuals who live in states where there has been expansion of Medicaid have better oncological outcomes," Mitchell said (*The Cancer Letter*, June 5, 2020; June 21, 2019). "So, we can say that African Americans and other underrepresented minorities, whether racial or ethnic, have access to the best health care and that we can, in a few years, show that there were no differences in individuals based on their ZIP code and where they live, and the color of their skin."

Often, African Americans can't afford and don't have access to the latest and greatest drugs and technologies.

"You get a system where, by innovating in a way that doesn't account for racism and doesn't account for other forms of discrimination, you actually perpetuate and exacerbate disparities," Chapman said.

"It's not surprising that when we come out with the next targeted agent, and that when those agents initially are only available in the context of clinical trials, we know that minorities—and especially black people—are less likely to go to hospitals that have expensive technologies, have these drugs available, have clinical trials available," Chapman said.

New treatments should be designed in a way that allows for access, Chapman said—"in ways that can be disseminated to hospitals that are not academic, that have a payer mix that is primarily Medicaid or for the uninsured."

Disparities remain—and grow—in part because people have learned to accept them.

"In other words, we have not only come, as a society, to accept that disparities will occur (as a law), but we can always explain them away by the differential distribution of individual risk factors (as the theory)," Winn wrote in an editorial about the very subject in COVID-19 (*The Cancer Letter*, May 11, 2019). "Thus, the 'individual risk factor theory' becomes a unifying, acceptable explanation and a refrain that is absolving from our collective, societal responsibility."

"To put it even more simply, underserved communities, are underserved, because they are underserved (as stated by Dr. Otis Brawley), and this has been made abundantly clear during the recent COVID-19 crisis."

People are paying attention because of the gruesome murder of George Floyd.

"I think we've gone through a radical transformation with the recent events. And I think that there's a better understanding from our university administration about what this movement means to our black community and our students," Siker said. "It's been great to see our administration step up and acknowledge that black lives matter in a public way, as well as support the students during this time."

Brawley is hopeful, too.

"You go to Missoula, Montana—where there are no blacks—but there's a Black Lives Matter protest. There were 300 people out for a Black Lives protest in Missoula, Montana, and they were all white," Brawley said. "The majority of people under the age of 50, who are white, actually are starting to get it, and not be threatened by it. Caring about other people, and not feeling threatened, can get us very far in this movement."

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# Q & A

Staudt and Wilson spoke with Matthew Ong, associate editor of The Cancer Letter.

CONVERSATION WITH THE CANCER LETTER

# BTK inhibitors improve COVID-19 outcomes by targeting upstream switch for inflammation, early data suggest

**Wyndham H. Wilson, MD, PhD,**
*Head, Lymphoma Therapeutics Section;*
*Senior investigator, Lymphoid Malignancies Branch;*
*Center for Cancer Research, National Cancer Institute*

**Louis M. Staudt, MD, PhD**
*Chief, Lymphoid Malignancies Branch;*
*NIH Distinguished Investigator;*
*Director, Center for Cancer Genomics,*
*Center for Cancer Research, National Cancer Institute*

Pondering hyperinflammation related to SARS-CoV-2, two NCI scientists had a hunch:

"It just dawned upon us, 'Hey, we know how to block inflammation,'" recalls Louis Staudt, chief of NCI's Lymphoid Malignancies Branch and director of the Center for Cancer Genomics.

Staudt and colleague Wyndham Wilson, head of the Lymphoma Therapeutics Section in NCI's Lymphoid Malignancies Branch, realized that they were staring at a potential role for Bruton tyrosine kinase inhibitors as a treatment for COVID-19-related cytokine release syndrome.

Staudt and Wilson have been working on BTK inhibitors, a class of lymphoma drugs, for over a decade before the COVID-19 pandemic hit.

The investigators immediately got in touch with AstraZeneca, the sponsor of the BTK inhibitor acalabrutinib (Calquence), and set out to assemble a multidisciplinary team of researchers to test the lymphoma drug in patients with severe manifestations of COVID-19.

Their findings were published June 5 in *Science Immunology*.

In a small study that enrolled 19 patients, the team of researchers found that the drug significantly improved oxygenation over a 10 to 14-day treatment course:

- Eight out of 11 patients (72.7%) that required supplemental oxygen had been discharged on room air,
- Four out of 8 patients (50%) no longer needed mechanical ventilation, with two out of the 8 patients (25%) discharged on room air.

Oxygenation in these patients often improved within one to three days, and no discernable toxicity was observed. Measures of inflammation—C-reactive protein and IL-6—normalized quickly in most patients, as did lymphopenia, in correlation with improved oxygenation.

"This was definitely a situation in which chance favored the prepared mind, as Louis Pasteur said. Wyndham and I had been just chatting, as we do, about medical things, and, obviously, we were chatting about COVID-19 and the inflammation that was getting people in serious medical trouble," Staudt, co-senior author of the study said to *The Cancer Letter*.

"We were struck by the biphasic clinical course in which some people infected with SARS-CoV-2 get fever and then get better, but other people, after initially getting better for a while, get this very severe lung inflammation," Staudt said to *The Cancer Letter*. "It was our prior experience with these drugs in cancer that led us to jump to realization that they might be effective in COVID-19."

AstraZeneca has initiated a randomized phase II/III study in 50 to 100 sites around the world. Another company, BeiGene is testing zanabrutinib, its version of a BTK inhibitor, in smaller studies.

"Despite this being a small study, the rapid and consistent improvement in these parameters in many patients and temporally associated with starting acalabrutinib appears quite convincing. Of course, our findings require confirmation in a randomized trial, which has been launched," Wilson, co-senior author of the study, said to *The Cancer Letter*.

"Once the safety component is completed—and we are hoping it will be completed in the next several weeks—[the AstraZeneca study] will then be expanded to a phase III double-blind randomized study involving around 500 cases," Wilson said. "Endpoints will be looking for improvement in oxygenation and clinical outcomes and, of course, inflammatory proteins. That will be a multi-national study. This is an international study."

Wilson and Staudt's research on BTK inhibitors grew out of their work on cancer patients that were getting fungal infections.

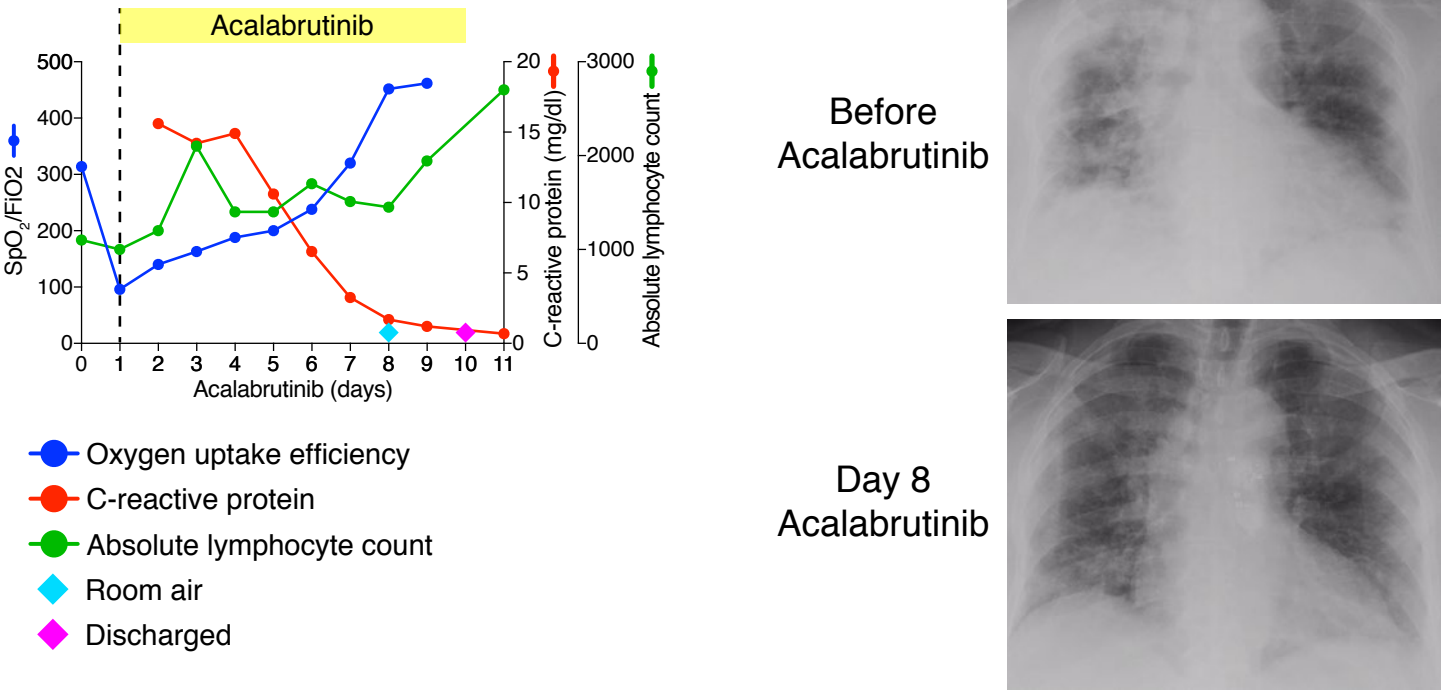
"This turned out to be quite specific to patients who had received high dose steroids for prolonged periods of time in our study of primary CNS lymphoma," Wilson said. "So, that observation led us to look at the effects of BTK inhibition in the innate immune system, as that is primarily responsible for control of fungal infections. That is neutrophils and macrophages."

Based on these early data, BTK inhibitors are expected to reduce or cut off the downstream production of inflammatory cytokines—e.g. IL-6 and IL-1—that play a major role in causing Acute Respiratory Distress Syndrome, the hyperinflammatory disease that makes COVID-19 especially deadly.

This effect will be studied in the late-stage trials that will enroll patients with severe COVID-19.

"Just metaphorically, treatment with tocilizumab and anakinra is like cutting the limbs off a tree, but treatment with acalabrutinib is like cutting the tree down from the trunk," Staudt said. "By analyzing blood samples from patients with COVID-19, we showed that the target of acalabrutinib, BTK, is active in the monocyte-macrophage lineage, which are innate immune cells that are abundantly present in the lungs of these patients.

"We also showed that in the blood, it is specifically the monocytes and not the other immune cells that have activated BTK and are making IL-6, an important cytokine in the cytokine storm




Acalabrutinib resolves pulmonary inflammation in severe COVID-19. – *Source: NCI*

that contributes to hyperinflammation in COVID-19."

Large phase III trials of IL-6 inhibitors—tocilizumab, sarilumab, and siltuximab—are underway. Under an NCI protocol, tocilizumab is available to cancer patients at institutions that are not participating in Genentech's phase III trial of the drug. The institute is also creating a registry of cancer patients with COVID-19 at over 1,000 sites in the U.S. (*The Cancer Letter*, March 27, April 10, April 17, 2020).

Patients with comorbid conditions appear to develop severe COVID-19, because their immune systems are chronically activated, leading to a rapid and overwhelming inflammatory response to SARS-CoV-2 infection, the researchers say.

"One area we have not discussed is the link between macrophages and the risk factors associated with severe COVID-19," Wilson said. "We have all seen the data that shows that patients at highest risk of severe symptoms are enriched by those with obesity, hypertension, and diabetes."

The phenomenon, in which the immune system is "marked" by previous exposures to foreign pathogens or medical conditions, is fairly well understood, Staudt said.

"It's not a genetic change in immune cells, but rather an epigenetic change. This phenomenon has been called 'trained immunity'. The immune cells are 'trained' by their previous exposures," Staudt said. "In the setting of COVID-19, the immune system may be trained by various comorbid medical conditions that chronically stimulate macrophages to change their epigenetic state. So, these trained immune cells may be on a hair trigger when something like SARS-CoV-2 comes around.

"That's a hypothesis. It's going to be fascinating to carefully study the function of macrophages in patients that have, or do not have, these comorbidities, and that's the science we'll be doing in the course of the recently launched randomized phase II/III CALAVI clinical trial."

Staudt and Wilson spoke with Matthew Ong, associate editor of *The Cancer Letter*.

**Matthew Ong: At first glance, your study comes across as very small, with only preliminary data. Even so, it seems to suggest significant improvement in outcomes. Could you describe your findings and what you've learned about using BTK inhibitors in patients with COVID-19?**

**Wyndham Wilson:** Let me start and say that it is a small series, but I think what is remarkable about this—particularly given that 18 of the 19 patients actually had worsening oxygen requirements when they started acalabrutinib—is that within several days of treatment with acalabrutinib, most patients showed a reduction in the C-reactive protein, improvement often to normal [levels] in the absolute lymphocyte count, and improvement in oxygenation.

Most of these patients were also receiving relatively high oxygen support, including high-flow oxygen or mechanical ventilation.

By the end of the study, 8 of 11 patients who were on supplemental oxygen no longer required oxygen and were discharged from the hospital. We also looked at the outcome after four more weeks of observation to assess if there were any recurrences, which we did not see.

Now, the group on ventilators was quite ill, in general. Some had been on a ventilator for extended periods and had multi-organ failure. But even within that group, there were four patients that showed a similar pattern of improved CRP, absolute lymphocyte count, and in fact, coming off the vent.

So, despite this being a small study, the rapid and consistent improvement in these parameters in many patients and temporally associated with starting acalabrutinib appears quite convincing. Of course, our findings require confirmation in a randomized trial, which has been launched.

**Louis Staudt:** When you see such a trial that is small and not controlled, you have to say, "Why do I believe this?"—and rightly so.

As Wyndham just said, the rapid effect of giving acalabrutinib on oxygenation and inflammation is a key finding, possibly suggesting causation. However, the additional and important concept is that we have a hypothesis for the action of acalabrutinib in COVID-19 and correlative evidence supporting the hypothesis.

By analyzing blood samples from patients with COVID-19, we showed that the target of acalabrutinib, BTK, is active in the monocyte-macrophage lineage, which are innate immune cells that are abundantly present in the lungs of these patients.

We also showed that in the blood, it is specifically the monocytes and not the other immune cells that have activated BTK and are making IL-6, an important cytokine in the cytokine storm that contributes to hyperinflammation in COVID-19.

So, when you put our clinical findings together with a mechanism of action that's plausible, I think and absolutely hope that when we complete the right study from a medical research point of view—a randomized controlled trial—we will find that acalabrutinib does indeed ameliorate severe COVID-19

**WW:** I think what makes our study stand apart from other studies is that we are targeting what we believe is the upstream instigator of inflammation. Studies of monoclonal antibodies that are directed at single cytokines, such as the IL-6 receptor and IL-1beta, are only targeting one of many inflammatory mediators. For example, in the case of tocilizumab, a monoclonal antibody against the IL-6 receptor, the CRP falls and oxygenation improves somewhat.

However, the blood concentrations of IL-6 actually rise, indicating that the source of the cytokine has not been quieted. It is likely the IL-6 rises due to a feedback mechanism, and this feedback may actually lead to increases in other cytokines that could obviate some of the benefits of blocking IL-6 action. Of course, this needs to be explored, but does illustrate potential issues with targeting single cytokines among the many that are increased in severe COVID-19.

Notably, inhibition of BTK also targets neutrophils as well. Indeed, these cells also produce cytokines and are replete in pathological specimens from the lungs of patients with COVID-19.

**LS:** Just metaphorically, treatment with tocilizumab and anakinra is like cutting the limbs off a tree, but treatment with acalabrutinib is like cutting the tree down from the trunk.

**The word "upstream" did come to mind, and I was just thinking of asking you about that.**

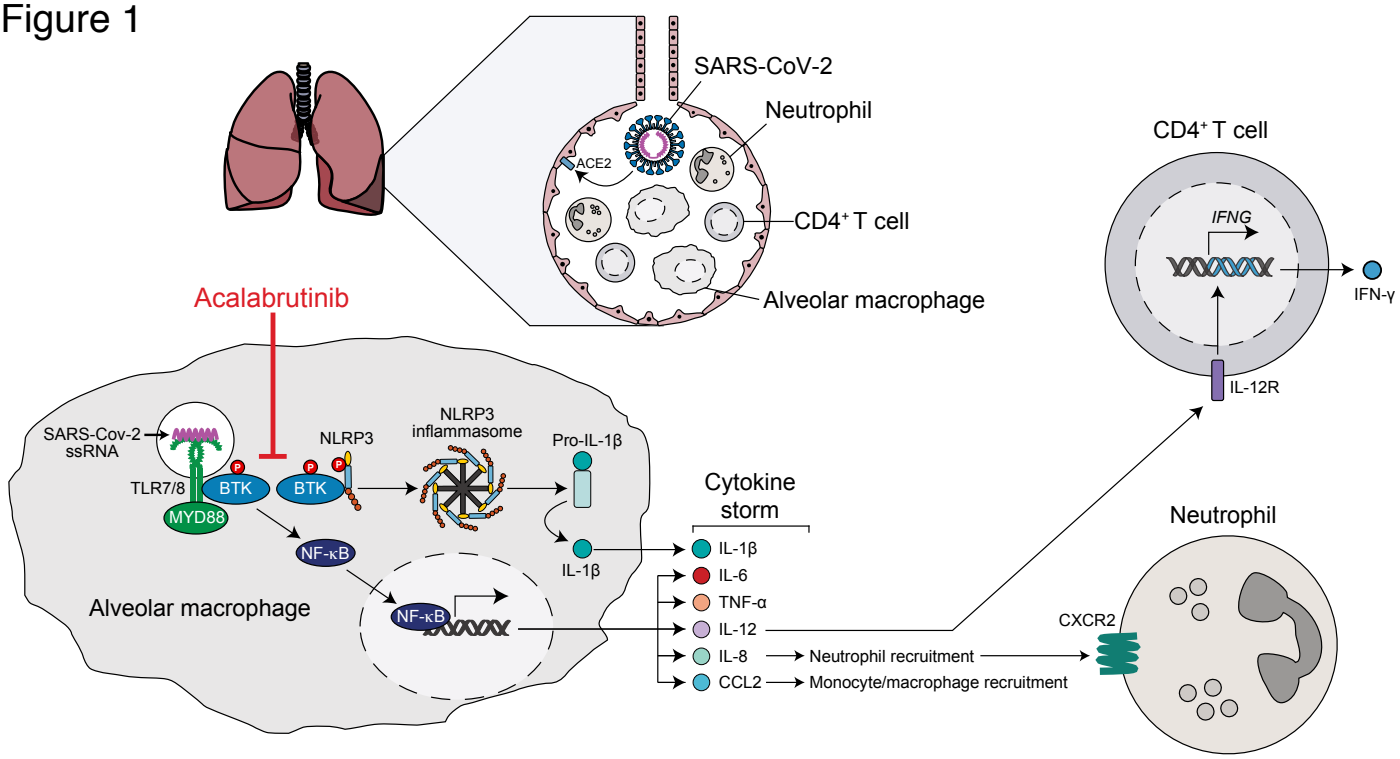
**LS:** It's very, very similar to the way we think about cancer. In cancer, we don't want to chase every small subclonal genetic mutation in a tumor. We want to get at the trunk of the tree—the oncogenic mechanisms that are engaged at the beginning of the cancer process.

The therapies that target those primary mechanisms are more likely to be successful than those that target secondary oncogenic processes. So, I think this is quite related to how one thinks about cancer therapy.

**WW:** I think that from a practical point of view, we should recognize that acalabrutinib and other BTK inhibitors are small molecules that are oral and relatively inexpensive compared to monoclonal antibodies.

Generally, BTK inhibitors also have a favorable safety profile, which is particularly true for acalabrutinib given its specificity for BTK and relatively low "off-target" effects. Indeed, we didn't see any safety issues, which was not unexpected given we only administered it for 10 to 14 days. You may know in cancer

Figure 1




Model of macrophage activation in severe COVID-19 leading to a cytokine storm. – *Source: NCI*

that this drug was developed for B-cell tumors, where it's given for months to years and generally is well tolerated.

**Could you explain the mechanistic relationship between acalabrutinib, the BTK inhibitor, and the reduction in production of IL-6 and other cytokines?**

**LS:** Matt, we spent a lot of time on Figure 1 of the paper. It's a drawing of a macrophage. What it shows is the presumed mechanism, namely that single strand viral RNA activates Toll-like receptors within the macrophage. These receptors activate the BTK kinase that then signals down to NF-kappa B, a transcription factor that turns on many of the cytokines, including IL-6, IL-12 and many others.

Separately, a fascinating new insight is that BTK activates the inflammasome, which is a molecular machine that is necessary to produce active interleukin-1 beta, another critical cytokine in the COVID-19 cytokine storm. BTK is directly associated with one of the subunits of the inflammasome, NLRP3, and induces that subunit to organize into large inflammasome structures that process and release interleukin-1 beta.

Our model is that BTK is ideally positioned to block all the signaling mechanisms that are contributing to the increased transcription of cytokines, or in the case of IL-1 beta, its processing into its secreted form.

That was a long explanation, but the picture in Figure 1 is worth a thousand words.

**I was following. This might be apples and oranges, but how do BTK inhibitors compare with some of the broad immunosuppressive agents that have been tested in patients with COVID-19?**

**WW:** I think the key here is to examine the targets of these other drugs and to consider what is known about cytokine release syndromes in COVID-19. In many ways, the hyperinflammatory response looks quite similar to what is known as macrophage activation syndrome.

Indeed, we hypothesized some years ago that BTK inhibitors might be useful in such syndromes, and even treated a

patient with HLH and observed a rapid reversal of the inflammation.

Apart from the downstream targeting of individual cytokines I discussed earlier, others have proposed drugs that target JAK/STAT signaling that is important for cytokine production.

Baricitinib targets JAK1 and JAK2 and is under investigation. While it is likely to quell some of the cytokine storm, it also inhibits T cell activation and is associated with viral reactivation and clots. It also has a complex and dual role in macrophage polarization to M1 (activate-inflammation) and M2 (inhibitory). Thus, in the setting of COVID-19, its effect on macrophages will be difficult to predict without further study.

We believe we have reasonable evidence for our model, which hypothesizes that the hyperinflammatory milieu of COVID-19 is dependent on macrophage-monocytes, based on two lines of evidence.

First, we show that inhibition of BTK is associated with a rapid decline in inflammatory proteins, including CRP and IL-6, and second, we show activation of BTK in blood monocytes, validating the activation of our target.

**JAK, as in Janus kinase?**

**WW:** Yes, Janus kinase. As I discussed earlier, JAK-STAT signaling is critical to many immune cells, including T cells and macrophages, and inhibition may have unpredictable effects.

And, of course, disabling T cell function could have adverse effects on viral control as observed when used in rheumatoid arthritis. And, of course, this all raises the question of whether the cytokine storm in COVID-19 is driven by T cells.

**LS:** Matt, using the previous metaphor, JAK inhibitors also cut off limbs of the tree. They would block IL-6 signaling, and signaling by other JAK-dependent cytokine receptors, so they would act downstream of the cytokine storm.

They would have no demonstrable effect on the macrophage, at least in the model that we have involving the Toll-like receptors and the inflammasome.

Just to say the obvious, steroids have not proven effective in previous coronavirus infections like SARS, and the World Health Organization does not recommend the use of steroids in SARS-CoV-2 infections.

We all know that the recent studies suggest that hydroxychloroquine is certainly not beneficial and may get some people in trouble.

I think the beauty of BTK inhibitors, which we have been studying because of their specificity for B-cell receptor signaling, is really that they only target an activated state of certain immune cells but don't hit more basic cellular functions.

I would say that the clinical experience with the safety of BTK inhibitors in thousands and thousands of patients suggests that they do not impair most normal immune responses, since treated patients only rarely get opportunistic infections. Rather, pathological situations involving intense activation of macrophages may be the setting in which BTK inhibitors could be helpful.

**WW:** One area we have not discussed is the link between macrophages and the risk factors associated with severe COVID-19. We have all seen the data that shows that patients at highest risk of severe symptoms are enriched by those with obesity, hypertension, and diabetes.

It is remarkable that these conditions are associated with macrophages where it has been shown they have activation of the NLRP3 inflammasone and have higher blood levels of CRP and IL-6. It is also known that fatty acids, via toll-like receptors, activate the inflammasone and likely play a role in the heightened inflammation found in these clinical conditions.

We have hypothesized that these clinical risk factors lead to a higher set point, if you will, in these patients and thus their macrophages are more sensitive to viral triggers via TLR receptors and development of a pathological hyperinflammatory state.

**So, basically their immune response is activated in a way that predisposes these high-risk patients to developing severe COVID with ARDS?**

**LS:** That's what we hypothesize. It's actually a fairly well-understood phenomenon in which the immune system is "marked" by its previous exposures to either infectious agents or to other medical conditions. It's not a genetic change in immune cells, but rather an epigenetic change.

This phenomenon has been called "trained immunity." The immune cells are "trained" by their previous exposures. In the setting of COVID-19, the immune system may be trained by various comorbid medical conditions that chronically stimulate macrophages to change their epigenetic state. So, these trained immune cells may be on a hair trigger when something like SARS-CoV-2 comes around.

That's a hypothesis. It's going to be fascinating to carefully study the function of macrophages in patients that have, or do not have, these comorbidities, and that's the science we'll be doing in the course of the recently launched randomized phase II/III CALAVI clinical trial.

**Speaking of which, what further studies are underway, and what are the next steps for studying BTK inhibitors in COVID-19 patients?**

**WW:** We engaged AstraZeneca, the manufacturer of this drug, very early on. They have now launched a randomized phase II/III study. The first component is a randomized phase II of 60 patients, which is an open label study in severe COVID-19 for safety purposes.

Once the safety component is completed—and we are hoping it will be completed in the next several weeks—it will then be expanded to a phase III double-blind randomized study involving around 500 cases.

Endpoints will be looking for improvement in oxygenation and clinical outcomes and, of course, inflammatory proteins. That will be a multi-national study. This is an international study.

Now, there are other smaller studies of BTK inhibitors.

**LS:** BeiGene has zanabrutinib as well.

**Are you looking at a minimum of about two months from now before preliminary results can be analyzed?**

**WW:** I would say two months would be a reasonable timeline. Correct.

**LS:** AstraZeneca is doing a full-court press on this and they're going to open the trial in 50 to 100 sites around the world.

**How do you plan to test the hypothesis we discussed earlier, to determine whether patient populations with hair-trigger immune systems would have a significant response to BTK inhibitors?**

**WW:** Well, there is a sub-study that's being run out of our group by Mark Roschewski and Mihalis Lionakis from NIAID where multiple translational endpoints will be explored.

Where possible, blood cells will be collected and analyzed for monocyte activation via phospho-BTK, IL-6 and response to TLR stimulation in multiple settings including patients who developed COVID-19 with few symptoms and those with severe symptoms and during and after recovery from the infection. We will also be looking at a host of cytokines and also gene expression profiling. Lou, do you want to comment?

**LS:** Yes, I think the truly big picture here is that, unfortunately, we have a situation where the entire human population is at risk of being exposed to a single infectious agent. Therefore, we have an opportunity to observe heterogeneity among human beings with respect to how their immune systems respond to the very same foreign pathogen.

So, we can directly get at the question of whether obesity affects the type of immune response that you mount. And the same question can be addressed in the setting of other COVID-19 comorbid conditions, such as diabetes, hypertension, and atherosclerosis. We will do those studies with our colleagues in NIAID, especially Mihalis Lionakis.

We will go well beyond just measuring cytokine levels. There will be an elaborate single-cell RNA-seq component to look at all the immune cells in the peripheral blood. There's going to be multiplex proteomic methods used as well to phenotype these immune cells. This will be a nice joint NIH effort, as has already been the case during our exploratory clinical study.

**That's a great segue into NCI's role in viral pandemics. How have decades of federally-funded work in cancer research led us to a point at which we can reliably use what we've learned to inform research into COVID-19?**

**WW:** You bring up a very good point. Lou and I have been working on BTK inhibitors for over a decade. During our work, we noticed that some patients were getting fungal infections. This turned out to be quite specific to patients who had received high dose steroids for prolonged periods of time in our study of primary CNS lymphoma.

So, that observation led us to look at the effects of BTK inhibition in the innate immune system, as that is primarily responsible for control of fungal infections. That is neutrophils and macrophages.

While that was not the primary focus of our work, obviously, we collaborated with Mihalis Lionakis in NIAID where he showed that inhibition of BTK in a murine model promoted aspergillus

infections and it was due to inhibition of the innate immune system.

Thus, it was our understanding of BTK's normal role in immunity that led us to our hypothesis in COVID-19 inflammation.

**LS:** I would just add that this was definitely a situation in which chance favored the prepared mind, as Louis Pasteur said. Wyndham and I had been just chatting, as we do, about medical things, and, obviously, we were chatting about COVID-19 and the inflammation that was getting people in serious medical trouble.

We were struck by the biphasic clinical course in which some people infected with SARS-CoV-2 get fever and then get better, but other people, after initially getting better for a while, get this very severe lung inflammation.

It finally dawned on us that we know how to block inflammation with the BTK inhibitors that we have studied for over 10 years in lymphoma. So, it was our prior experience with these drugs in cancer that led us to jump to realization that they might be effective in COVID-19, which is supported by our small clinical study and we hope and expect will be confirmed in the ongoing randomized trial.

> “It finally dawned on us that we know how to block inflammation with the BTK inhibitors that we have studied for over 10 years in lymphoma.”
>
> *– Louis Staudt*

The other thing I would like to say, especially for *The Cancer Letter*, is that cancer is a significant risk factor for getting bad COVID. Though more work is needed, a paper from Chinese researchers reported that patients with blood cancers and lung cancers had the highest relative risk for developing severe COVID.

That really resonated with me, because the blood cancers are obviously derived from the immune system, and they consequently can secrete cytokines and interact with normal immune cells in ways that may train the immune system, as we were discussing earlier. That may be why SARS-CoV-2 infection triggers a hyperinflammatory response in these patients. This needs to be studied fully.

The National Cancer Institute itself, as you may know, is going to start a registry of patients with cancer who get COVID-19, and follow them over several years to see, number one, how they do with the COVID-19 and number two, see how they do with their cancer, having had COVID-19.

I think that's an interesting open question.

# Fajgenbaum gained insight into COVID-19 while seeking treatment for Castleman disease (which he has)

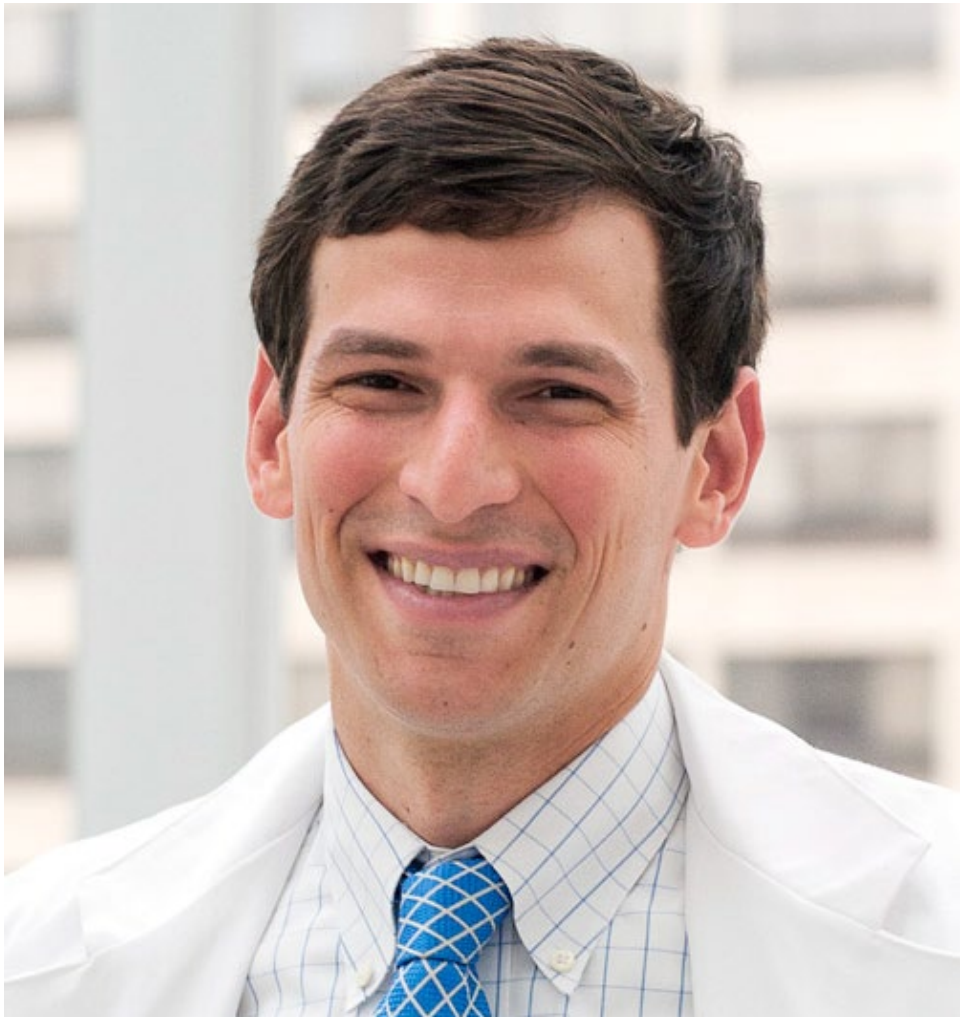
*By Alexandria Carolan*

David C. Fajgenbaum knows all about facing the unknown.

Fajgenbaum wasn't expected to live more than 5 years once he was diagnosed with idiopathic multicentric Castleman disease in 2010. He experienced multiple organ failure, he's been through cytokine storm syndrome, and he has had chemotherapy.

Over the years, Fajgenbaum, now assistant professor of translational medicine and human genetics, and associate director of patient impact with the University of Pennsylvania Orphan Disease Center, exhausted every treatment option available for the disease before he began conducting his own research—which ultimately saved his life.

Research for IMCD includes study of interleukin-6 inhibitors, agents used to treat the cytokine storm. Now, it appears that the science of cytokine storm syndrome associated with IMCD mirrors that of massive cytokine release in COVID-19. Fajgenbaum has pivoted his research toward IL-6 inhibitors for use in the COVID-19 setting.



"Our opening ceremony speaker used his own disease and his own scientific quest in exactly that way. He pivoted from his disease to COVID-19, because of the commonalities they shared," Chief Executive Officer of the American Society of Clinical Oncology Clifford A. Hudis said to *The Cancer Letter* (*The Cancer Letter*, June 5, 2020).

In his lecture May 30, during the opening session of ASCO's virtual annual meeting, Fajgenbaum focused on his experiences living with Castleman disease, research into the disease, and its overlap with COVID-19. Fajgenbaum is also the author of *Chasing My Cure: A Doctor's Race to Turn Hope into Action; A Memoir.*

"With the overlap between COVID-19 and IMCD both clinically and therapeutically, I decided to refocus my lab in March to systematically track all off label treatments being used against COVID-19, and to follow our blueprint to search for new drugs that can be repurposed," said Fajgenbaum, who is also executive director at Castleman Disease Collaborative Network and founding director at the Center for Study & Treatment of Lymphadenopathies & Cytokine Storms at the University of Pennsylvania. "We found approximately 150 drugs have already been tried in the first 15,000 COVID-19 patients that we've studied."

Overlap of drugs can be found at cdcn.org/corona.

## Castleman disease

In 2012, about $10,000 a year was dedicated toward research. NIH funding for the disease didn't exist. There as no research infrastructure, and idiopathic multicentric Castleman disease—which Fajgenbaum was diagnosed with—had no diagnostic criteria, treatment guidelines, cell lines, model systems, or biobanks.

"I knew I wouldn't make it to our wedding day unless I found a drug to keep me in remission, so I dove headfirst into research," Fajgenbaum said. "At this stage, I had failed to respond to all drugs that had ever been given to patients with my disease, and I began searching for a novel approach."

> I knew I wouldn't make it to our wedding day unless I found a drug to keep me in remission, so I dove headfirst into research. At this stage, I had failed to respond to all drugs that had ever been given to patients with my disease, and I began searching for a novel approach.
>
> *– David C. Fajgenbaum*

In 2020, Castleman disease has $1.4 million in translational research funding, and an additional $10.1 million in external funding. NIH provided the first IMCD research grant to Fajgenbaum's lab recently.

"We went from having two advocacy organizations to now having one central collaborative network with a unified research infrastructure and also collaborative research agenda," Fajgenbaum said. Altogether, over 1,200 patients are listed in the contact registry.

How does this research apply to COVID-19?

"[IL-6] is now being used with some anecdotal success against COVID-19, where drug repurposing provides our greatest hope in the short-term before a vaccine is developed," Fajgenbaum said. "Tocilizumab is such a great example of focused research in drug development within a rare disease being spread to many other diseases."

Fajgenbaum mapped results from cytokine panels in the months leading up to his most recent relapse, just before his wedding. He found that 2 of the 13 cytokines measured began to rise months before the flare-up.

"One was soluble IL-2 receptor, a marker of T cell activation, and the other was VEGF. We confirmed the increased T cell activation and VEGF levels by serum proteomics and flow cytometry," Fajgenbaum said.

As Fajgenbaum finds more ways to potentially treat IMCD—and now, COVID-19, he is most focused on his own remission.

Nothing is certain.

"After nearly dying five times in my first three-and-a-half years after diagnosis, I've been in remission for 76.81 months," Fajgenbaum said. "I say 76.81 months, because I know I can't round up. I may relapse and be in the ICU tomorrow. But I also refuse to round down, because my team of physicians and researchers have fought so hard for every day of remission."


GUEST EDITORIAL

# Impact of COVID-19 on Georgia's community providers: a snapshot from Georgia NCORP

**By Guilherme Cantuaria, MD, PhD**
*Principal investigator, Georgia NCORP,*
*Chair, Gynecologic Oncology Steering Committee, Northside Hospital Cancer Program*

As we approach the middle of June, Georgia appears to have come to the other side of its COVID-19 curve. Available information from the Georgia Department of Health reveals Georgia has nearly 54,000 confirmed COVID-19 cases, with the heaviest concentration of cases in the metro Atlanta area (as a result of population size, not density).

The Georgia NCORP Community Site, established in 2014, serves a broad population of Georgia's cancer community and represents a collaboration between the largest community oncology clinical trial programs in Georgia—Northside Hospital Cancer Institute (NHCI) in Atlanta, the Nancy N. and J.C. Lewis Cancer & Research Pavilion (LCRP) at St. Joseph's/Candler in Savannah, and the Georgia Center for Oncology Research and Education in Atlanta. Georgia CORE provides network affiliation for four actively accruing healthcare organizations across the state: Northeast Georgia Medical Center (Gainesville), Navicent Health (Macon), John B. Amos Cancer Center (Columbus), and Harbin Clinic (Rome).

We surveyed our GA NCORP partners and affiliates to ascertain the impact of the COVID-19 pandemic and the shelter in place orders on daily practice and trial participation. Areas addressed in the survey included the use of telemedicine, surgery, ambulatory cancer care and testing, personal protective equipment, the impact on clinical research, and staffing.

Telemedicine has become widely incorporated into GA NCORP sites during the COVID-19 pandemic, as high-risk cancer patients are reluctant to risk visiting healthcare facilities for in-person appointments.

Our providers agree that while telemedicine has its utility and patients currently seem to enjoy it, its practice interferes with productivity and consumes more time than in-person visits. Insurance reimbursement will likely dictate the

continued use of telemedicine in the long-term. While there will certainly be a role for telemedicine post-pandemic, it will likely be to a much lesser extent.

At least three of our providers, who comprise 98% of the GA NCORP accruals (NHCI, LCRP, and NGMC), adhered to the American College of Surgeon's COVID-19 Recommendations for Management of Elective Surgical Procedures, which were released mid-March. Elective surgical volumes at these sites dropped to as low as approximately 20%.

As the curve of COVID-19 infection plateaued and began to flatten, surgical procedures were phased in to approximately half their pre–COVID-19 volume. With Georgia's reopening phase now in full swing, most sites continue to build back surgical volume by resuming all elective surgeries (though not at pre-pandemic levels yet).

Significantly, surgery was not rescheduled in cancer cases where the delay of the surgical procedure could affect outcome.

> Our providers agree that while telemedicine has its utility and patients currently seem to enjoy it, its practice interferes with productivity and consumes more time than in-person visits.

For the most part, ambulatory cancer treatment was not impacted by the COVID-19 pandemic. Chemotherapy infusions were still administered, with minimal change in volume; however, strict policies were implemented to protect patients and staff.

The changes included appointment check-in from the patient's vehicle, temperature check and screening prior all visits, a strict no family or visitors policy, social distancing, and the universal mandatory use of face masks.

Pre-chemotherapy testing for COVID-19 was not instituted at any sites prior to treatment infusions, unless it was warranted based on clinical screening. Of interest, one site saw an apparent increase in new lung cancer diagnoses stemming from individuals seeking medical care for suspected COVID-19, which turned out to be cancer.

All members had strong concerns about the availability of PPE, especially N95 masks (which became scarce at a few sites); therefore, measures were put into place very early to preserve equipment. Fortunately, availability of PPE and preservation measures (e.g., strict inventory control, re-use, decontamination of masks) prevented the manifestation of a dire situation.

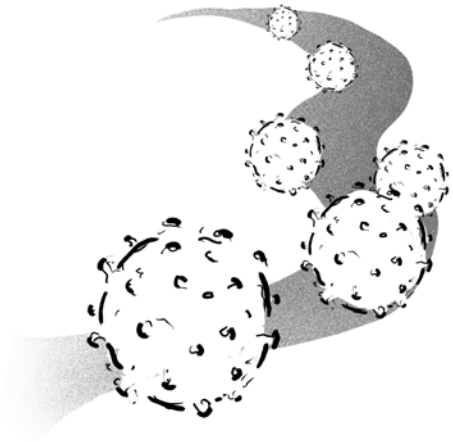
Clinical trial accrual took a nosedive among our sites from March and April (see table). With the exception of a treatment trial that presented the best option for a patient, all research (including screening, CCDR, cancer prevention, and cancer control) was put on hold. Screening trials have been the first to be phased back in, with all research resuming and trials reopening in mid-May. We are working through extensive plans to safely re-engage research.

Lastly, GA NCORP was fortunate to have avoided any significant furloughs or mandatory redeployment. Some nurses and staff were voluntarily placed in different functions, but we are in the process of resuming normal staffing operations.

Our Community Site has learned a lot about managing patients with cancer during a pandemic in a short time, but we have all risen to the challenge and have put systems in place to continue our important research in a safe manner moving forward.

| Accruals / Activity | Month | 2019 | 2020 |
|---|---|---|---|
| All Accruals (excludes DCP, TMIST & CCDR) | March | 19 | 10 |
| | April | 11 | 5 |
| TMIST Accruals | March | 75 | 32 |
| | April | 76 | 0 |
| DCP-001 Activity | March | 67 | 37 |
| | April | 69 | 2 |
| CCDR Activity | March | 0 | 2 |
| | April | 2 | 0 |

COVID-19 UPDATES



## Guidance helps select breast cancer patients for urgent surgery or chemotherapy during pandemic

A new approach to better select breast cancer patients in need of urgent surgery or chemotherapy during the COVID-19 pandemic has been developed by researchers at The Royal Marsden and the Breast Cancer Now Research Centre at The Institute of Cancer Research, London, in collaboration with colleagues in the U.K., Germany, and the U.S.

The innovative algorithm, using data from multiple international trials, can identify postmenopausal patients with primary ER+HER2- breast cancer (c.70% of cases) who have less endocrine-sensitive tumours and who should be prioritised for early surgery or neoadjuvant chemotherapy.

The COVID-19 pandemic has led to an international need to prioritize the number of cancer surgeries and chemotherapy treatments to the most urgent patients to protect staff and vulnerable patients. While patients diagnosed with triple negative and HER2-positive breast cancer have still been going forward for urgent surgery or chemotherapy, for a large group of patients deferring these treatments and prescribing neoadjuvant endocrine therapy, i.e. treatment to reduce the stimulation of the disease by estrogen without the surgical removal of the breast tumor, has been identified as the best course of treatment.

Development of the new treatment algorithm was led in the UK by researchers working in the Ralph Lauren Centre for Breast Cancer Research at The Royal Marsden and the Breast Cancer Now Toby Robins Research Centre at The Institute of Cancer Research.

Prof. Mitch Dowsett, head of the Ralph Lauren Centre for Breast Cancer Research at The Royal Marsden and Professor of Biochemical Endocrinology at the ICR, led the collaboration published in NPJ Breast Cancer this week. The work highlighted that while 85% of patients in whom treatment by surgery is deferred would be safe to remain on NeoET treatment for up to six months, 15% can be identified who are resistant to this treatment and risk disease spread.

"NeoET can block the tumor from growing successfully for many women but for one in six who are resistant there is a risk the tumor will continue to grow and spread elsewhere," Dowsett said in a statement.

"By accessing unpublished results from clinical trials involving thousands of patients, with colleagues here and abroad we have developed a new way of directing patients' treatment in this global crisis. Using the data on estrogen receptor, progesterone receptor and proliferation from the tumor of newly diagnosed patients, our simple new calculator can be used by fellow clinicians worldwide to immediately identify the best course of treatment for about 80% of their patients.

"Then, by drawing upon our earlier research, we can help the other 20% by measuring Ki67 (a protein that measures the number of cells dividing in the tumor) a few weeks after starting their NeoET. Overall, we can identify the 15% of the women who are most at risk of relapsing on just NeoET treatment and should be prioritised for surgery or neoadjuvant chemotherapy.

## ChristianaCare develops COVID-19 symptom monitoring, testing program for businesses and employers

ChristianaCare has developed a virtual telehealth service that provides daily monitoring of employees for COVID-19 symptoms, testing, and care for employees who test positive.

The Employee COVID-19 Symptom Monitoring and Testing Program is designed to increase safety and ease anxiety in the workplace. Employees will have access to a registered nurse to discuss their symptoms and the opportunity for a tele-visit with a provider.

The program relies on ChristianaCare's COVID-19 Virtual Practice and its CareVio care management program for daily bi-directional, secure text messaging.

Currently, 12 employers in Delaware, Pennsylvania, New Jersey, Louisiana and Arizona are using the ChristianaCare Employee COVID-19 program. All told, the program is monitoring nearly 5,000 people.

Prior to the start of work each day, employees receive a text message in English or Spanish with a few screening questions related to coronavirus symptoms. If employees indicate they have no symptoms, they receive an "All Clear" text that it is safe to report to work. If they indicate they have developed symptoms, they will receive a message that they are "Not Cleared" and should not report to work. A registered nurse from the CareVio team will reach out for further evaluation.

If the nurse identifies positive coronavirus symptoms, employees are urged to see a provider in ChristianaCare's COVID-19 Virtual Practice through a tele-visit or visit their own primary care provider. If employees choose the COVID-19 Virtual Practice, they may be sent for a test. If the test is positive and they have symptoms of coronavirus, CareVio will monitor them several times each day to make sure they are improving. If symptoms progress, CareVio will arrange for another tele-visit with the COVID-19 Virtual Practice.

The COVID-19 Virtual Practice began mid-March 2020 within ChristianaCare's Center for Virtual Health. Through June 1, the practice has conducted more than 2,536 virtual visits with more than 2,070 patients.

## HealthTree recruits over 1,000 participants for study on impact of COVID-19 on MM

A total of 1,066 patients have joined a HealthTree observational study on COVID-19 and multiple myeloma. All participating patients have filled out a HealthTree profile by contributing their de-identified health data and answered survey questions related to their outcomes during the COVID-19 pandemic.

The aim of the study is to help patients and physicians use real data to drive future medical decisions.

The study was first announced on April 16, 2020. The anonymous answers will be aggregated and analyzed by myeloma researchers to identify recommendations for patients navigating myeloma during the COVID-19 pandemic. Initial study results will be available in July, and more extensive results will be published in December.

IN BRIEF


## ACS eliminates 1,000 positions due to fundraising drop

The American Cancer Society is reducing its overall budget by approximately 30%, with cuts to non-personnel and personnel expenses as a result of a decrease in fundraising revenue.

ACS eliminated 1,000 positions across the U.S.

"We are also making a fundamental shift in how we engage and serve communities. Within a very short period of time, we had to reconfigure our entire portfolio to honor donor dollars and continue to advance our mission amid these very difficult times," ACS officials said in a statement. "We will continue to engage with people where they live their lives, with a greater emphasis on the digital world in which we live."

## ASCO's CancerLinQ launches SmartLinQ QOPI Certification Pathway

ASCO's CancerLinQ launched the SmartLinQ QOPI Certification Pathway, an application that allows oncology practices to automate quality measure tracking and reporting for participation in ASCO's Quality Oncology Practice Initiative Certification Program, a three-year certification recognizing practices' commitment to high-quality care for outpatient oncology practices.

Since 2019, SmartLinQ has enabled CancerLinQ practices to automate their quality activities, derive actionable insights from real-world patient data, and benchmark their care against the CancerLinQ network. The new SmartLinQ QOPI Certification Pathway was recently piloted at four of CancerLinQ's more than 100 subscribing practices, enabling them to reduce staff time and expenses for quality reporting for QOPI Certification. It is now available for re-certification and maintenance submissions for all QOPI Certified CancerLinQ subscribers.

SmartLinQ's benefits stem from the automation of quality management functions, beginning with data collection. CancerLinQ automatically and securely takes in and harmonizes and codifies the data from practices' electronic health record systems, eliminating the need for manual chart abstraction for

quality programs like QOPI Certification. New Mexico Cancer Center, one of the SmartLinQ QOPI Certification Pathway pilot practices, saved approximately 100 hours of staff time when using SmartLinQ to automate its recertification for the QOPI Certification Program.

Beyond data abstraction and automated quality reporting for QOPI Certification, SmartLinQ enables practices to:

- Track progress daily against a broad set of quality measures, both for the practice overall and for specific sites and individual physicians
- Benchmark care against peers, by querying de-identified patient data on 1.5 million real-world cancer patient records in the CancerLinQ database
- Identify "actionable patients" who still need specific care or treatment to comply with quality standards, creating opportunities to proactively improve care
- Identify and fix data quality issues, such as missing or inaccurate data in patients' EHRs.

## UCLA Health launches telehealth genitourinary cancer genetics program

UCLA Health and the Department of Urology at UCLA have created a new telehealth cancer genetics program that will provide rapid access to high-quality genetic counseling and testing.

The program, which officially launches June 29, 2020, will focus on diagnosing hereditary kidney, bladder, testicular and prostate cancers. The program hopes to complement and expand on the work providers at the UCLA Jonsson Comprehensive Cancer Center have already developed.

There is a national shortage of genetic counselors, potentially impacting clinical outcomes of those who are diagnosed. In partnership with Genome Medical, this service will augment current efforts of UCLA genetic counselors to keep up with the rapid increase in new criteria for genetic testing.

## Rogel Cancer Center team gets $2M grant to train researchers in cancer care delivery

University of Michigan Rogel Cancer Center researchers received a $2 million grant from NCI to prepare the next generation of scientists focused on cancer care delivery.

This new training program focuses on preparing pre- and postdoctoral trainees from diverse disciplines to become independent investigators researching how cancer care is delivered and how to improve the care experience for patients with cancer.

"Recent advances in cancer therapies may be irrelevant if they cannot be given in a safe, effective, efficient, equitable and patient-centered manner across diverse treatment settings. We need more researchers to help discover care gaps, develop and test efficacious interventions, and implement discoveries into routine clinical practice," principal investigator Christopher Friese, associate director for cancer control and population sciences at the Rogel Cancer Center and Elizabeth Tone Hosmer Professor of Nursing at the U-M School of Nursing, said in a statement.

The grant will fund a total of three predoctoral and fourteen postdoctoral students. With the support of their mentors, formal coursework, selected emphasis activities and professional socialization, trainees will acquire skills in descriptive discovery research, intervention development and testing, and implementation science to address gaps in the field.

The first predoctoral student and initial four postdoctoral students have been selected and will begin their training July 1.

## Zakrzewski, Gyurkocza, Feinman receive MSK/ Hackensack Meridian Health funding for immunology research

Memorial Sloan Kettering and Hackensack Meridian Health have formed an Immunology Research Collaboration as part of their partnership. Through this joint initiative, researchers can apply for funding to support immunotherapy research.

The three researchers with projects selected in 2020 for funding support over one to two years are:

- **Johannes Zakrzewski**, associate member in the Hackensack Meridian Health Center for Discovery and Innovation, is leading the project "Targeting Auto and Neoantigens with In Vivo-Generated Antigen-Specific T Cells." Through this project, his lab will investigate novel strategies for cancer immunotherapy and immunosurveillance by employing the capacity of the thymus gland in mice to produce cancer-targeted T-cells, and by harnessing advances in gene therapy and chimeric antigen receptor technology to help lay the groundwork for future cancer immunotherapy treatment options that are safe and durable. This immunotherapy approach could be especially suitable for children and young adults with cancer.

- **Boglarka Gyurkocza**, a Memorial Sloan Kettering medical oncologist, is leading the project "Targeting the Gut Microbiome to Improve Outcomes after Allogeneic Hematopoietic Cell Transplantation." This project will explore in an ongoing clinical trial whether certain antibiotics preserve specific anaerobic intestinal microbiota in patients who have received stem cell transplants, and how preserving this gut flora affects the risk of patients developing graft-versus-host disease, a serious complication of stem cell transplant. The trial is currently open at MSK and will also open at the John Theurer Cancer Center. Gyurkocza and colleagues will also examine how the loss of anaerobic gut flora may impact the risk of relapse and progression in multiple myeloma mouse models.

- **Rena Feinman**, associate member in the Hackensack Meridian Health Center for Discovery and Innovation, is leading a project called "Impact of the Gut Microbiome on Immunotherapeutic Response in Multiple Myeloma." Feinman and the project team will investigate whether distinct gut microbiota can predict the risk for relapse in patients with high-risk multiple myeloma who received the standard of care, including a stem cell transplant from a donor. By analyzing the gut microbiota in patients' stool before and after transplant, the researchers will also be able to personalize which antibiotics a patient receives. Feinman will also explore the relationship between the gut microbiome and multiple myeloma progression in experimental models.

## TGen's Ashion Analytics certified for NCI's MATCH cancer clinical trials

Ashion Analytics, a clinical laboratory of the Translational Genomics Research Institute, an affiliate of City of Hope, is now part of NCI's MATCH program, which provides patients who have rare or difficult-to-treat cancers with access to unique clinical trials nationwide that might give them the best therapeutic treatments and outcomes.

Ashion is one of the nation's few dozen institutes participating in MATCH—Molecular Analysis for Therapy CHoice.

Ashion screens cancer patients for all of the nearly 3 billion nucleotides, or letters, in human DNA, which includes more than 19,000 genes. Ashion accomplishes this by performing genomic sequencing—a molecular-level analysis of each patient's entire genome. Ashion scientists then match each patient's unique cancer to the best available cancer treatments.

Ashion uses a proprietary test called GEM ExTra, which covers all protein coding regions of DNA, and an analysis of all RNA.

Using GEM ExTra, Ashion sequences both the individual patient's normal genome and the patient's cancer genome. Then the two sets of genomic data are compared to find the gene changes, known as mutations, that are specific to the tumor and may be potentially driving that patient's cancer.

FUNDING OPPORTUNITIES


## EGFR Resisters/ LUNGevity issues RFA for FY21 award program in EGFR-positive lung cancer research

EGFR Resisters and LUNGevity Foundation have issued a Request for Application for the EGFR-Positive lung cancer research program.

Funded research is expected to include at least one aim that is translational and must be directly related to improvement in patient outcomes and/or lead to a clinical trial. The EGFR-Positive award is open to researchers at U.S. and international institutions. At the time of application, an international candidate must name a co-principal investigator who is employed at a U.S. institution. A successful applicant may receive up to $200,000 over an award term of two years.

The Request for Applications will be posted as of June 18 on the LUNGevity website and on the proposalCENTRAL website. For more information, contact Margery Jacobson at mjacobson@LUNGevity.org or 312-407-6109.

## DoD announces FY20 anticipated funding opportunities

The FY20 Defense Appropriations Act provides funding to the Department of Defense Pancreatic Cancer Research Program to support pancreatic cancer research.

The funding is directed by the Office of the Assistant Secretary of Defense for Health Affairs, the Defense Health Agency J9, Research and Development Directorate manages the Defense Health Program Research, Development, Test, and Evaluation appropriation. The managing agent for the anticipated Program Announcements/ Funding Opportunities is the Congressionally Directed Medical Research Programs at the U.S. Army Medical Research and Development Command.

The PCARP is providing the information in this pre-announcement to allow investigators time to plan and develop ideas for submission to the anticipated FY20 funding opportunity. This pre-announcement should not be construed as an obligation by the government. The FY20 PCARP Program Announcements and General Application Instructions for the following award mechanisms will be posted on the Grants.gov website. Pre-application and application deadlines will be available when the Program Announcements are released.

For more information, visit http://cdmrp.army.mil/.

# The First International Summit on Interventional Pharmacoeconomics

Finding Solutions to High Drug Costs

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***ZOOM Web Conference June 29 – July 1, 8am-1pm ET daily***

## SESSION TOPICS

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HIGH- VALUE OPPORTUNITIES

CLINICAL TRIAL DESIGN: STATISTICAL OPTIONS/CHALLENGES

BIOSIMILARS AND PATENT ISSUES

CREATING THE INFRASTRUCTURE FOR INTERVENTIONAL PHARMACOECONOMIC TRIALS

OPPORTUNITIES TO OPTIMIZE CANCER DRUG POLICIES

THE INTERVENTIONAL PHARMACOECONOMIC TOOLBOX

FOCUS ON OPTIMAL DOSING OF IBRUTINIB

## WELCOME ADDRESS

**Allen Lichter**
Value in Cancer Care Consortium

## KEYNOTE SPEAKER

**Cliff Hudis**
American Society of Clinical Oncology

## Web Conference Organizers

Daniel Goldstein, MD – Davidoff Center, Rabin Medical Center, Israel
Mark J Ratain, MD – The University of Chicago

## Hosted by:

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# INTERVENTIONAL PHARMACOECONOMICS: REDUCING THE IMPACT OF HIGH GLOBAL DRUG COSTS

Mark J. Ratain [1,2], Daniel A. Goldstein [2,3], Garth W. Strohbehn [1,2], and Allen S. Lichter [2]
University of Chicago Medicine, Chicago, IL [1], the Value in Cancer Care Consortium, Ann Arbor, MI [2], and Clalit Health Services, Tel Aviv-Yafo, Israel [3]

The Value in Cancer Care Consortium, University of Chicago Medicine and Clalit Health Services have organized the 1st International Summit on Interventional Pharmacoeconomics, which will be a global live Zoom event on June 29 to July 1 from 8 am to 1 pm Eastern Time daily. The daily, 5-hour event (with each day comprised of three sessions) was carefully scheduled to facilitate live participation in most global time zones. The opening session will include a keynote address by Clifford Hudis, CEO of ASCO, entitled "Are cancer drug prices in the US the problem or the symptom?", as well as an overview of interventional pharmacoeconomics – the application of clinical pharmacology's best principles to modern oncology drugs in an effort to develop off-label, lower cost, and equally efficacious treatment regimens. Subsequent sessions will discuss specific drugs (e.g., abiraterone, ibrutinib, trastuzumab, nivolumab) and malignant diseases (e.g., multiple myeloma, chronic myelogenous leukemia), and even COVID-19.

There will also be sessions on biosimilar and patent issues (including Sarah Yim of FDA), global policy issues (including speakers from around the world), and mechanisms to promote interventional pharmacoeconomic studies (with representation from a variety of global healthcare systems). The final session will be focused on the optimal dosing of ibrutinib, a topic that this newsletter has covered in depth in the past.

The rapidly increasing costs of oncology drugs have contributed to the spiraling costs of healthcare in general, with consequences for access and adherence. Even healthy employees suffer from the rising costs of drugs, as these increased healthcare costs function as a regressive tax, since total compensation rises but salaries are relatively flat.

The cost of cancer care is increasing at an alarming rate. While there have been many proposals in the US to flatten or bend the cost curve, little has happened, and costs, especially drug costs, continue to rise. One way to address this problem is to use drugs more wisely. Most new, expensive, targeted drugs are labeled to be used in doses far in excess of what is required to achieve their biologic effect. Through interventional pharmacoeconomic investigation we can easily save billions of dollars annually from drug spend, lessening the level of financial toxicity for patients and families. Furthermore, for some drugs (e.g., ibrutinib), lower doses may have a superior therapeutic index, with the same efficacy but lower off-target adverse events.

Against the backdrop of a global pandemic and long-overdue efforts to ensure access to and equity of cancer care, the 1st International Summit on Interventional Pharmacoeconomics is timely, and with an exciting list of speakers and topics, we urge you to register and join us. Please note that as this is a Zoom event, we will be limited to 500 participants each day.

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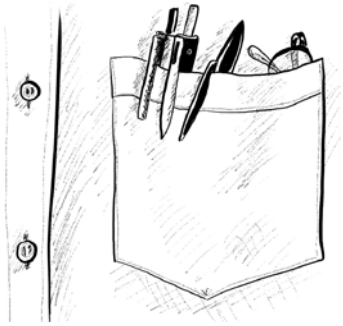
THE CLINICAL CANCER LETTER



TRIALS & TRIBULATIONS

# As screening declines amid COVID-19, at-home stool DNA test for CRC gets high adherence in Medicare population

**By Paul J. Limburg, MD, MPH**
*Chief medical officer for screening, Exact Sciences;*
*Consultant, Division of Gastroenterology and Hepatology, Mayo Clinic*

In the midst of the heavy burden COVID-19 has placed on the health care system, cancer remains relentless. The already difficult journey for cancer patients has become more uncertain as the ways we provide and access healthcare have changed to accommodate measures that protect both health care providers and cancer patients from COVID-19.

Finding an appropriate balance between the near-term challenges imposed by the current pandemic and the longer-term consequences of delayed health care in other areas, such as cancer screening, requires thoughtful consideration and broad-based collaboration.

Recent reports indicate that nearly one third of Americans have put off at least some component of their health care due to the current environment.[1] With respect to colorectal cancer—the second leading cause of cancer death in the U.S.[2]—delays in preventive healh care, including colorectal cancer (CRC) screening, could lead to later-stage diagnoses and increased mortality rates, rapidly eroding years of steady progress in CRC screening, early detection and successful treatment.[2]

In various roles over my 20-plus year career, including practicing gastroenterologist, cancer prevention investigator, and chief medical officer for Screening at Exact Sciences, I have found that successful CRC screening requires access to accurate, acceptable tests, as well as patient and provider commitment

to completing the selected screening strategy, including follow-up diagnostic evaluation, when indicated.

Each of these components is critical to consider, now more than ever, as we are faced with newly-raised questions: Are the usual CRC screening tests available in the pandemic environment? Will patients be receptive to CRC screening amidst other concerns? Will providers have the bandwidth to embrace preventive care as a priority? Even before COVID-19, it was estimated that 53,000 people would die from colorectal cancer in 2020.[2] It is important that we, as a community, provide respectful and responsible guidance to these questions now, so that the benefits of timely preventive care can be optimized.

There are several guideline-endorsed test options for average-risk CRC screening, including endoscopic, radiologic, and stool-based tests. Each screening modality has strengths and limitations, leading the US Preventive Services Task Force[3] and the American Cancer Society[4] to offer a menu of recommended strategies without a rank order, preferring instead to emphasize patient and provider choice in selecting the option that will most likely be completed.

Noninvasive CRC screening tests, including the fecal immunochemical test (FIT) and the multi-target stool DNA (mt-sDNA or Cologuard) assay, are widely accepted and offer a way for patients to safely screen at home, both during and after the current COVID-19 pandemic.

Completion of stool-based testing now can also help to reduce the pending backlog in endoscopic and radiologic CRC screening exams that have limited availability until a new version of normalcy returns. While the pandemic has created complex challenges without easy solutions, broad-based collaboration to achieve common public health goals represents the best way forward.

## Achieving colorectal cancer screening adherence

In an uncertain time where cancer screenings and other diagnostic panels have fallen by as much as 68% nationally, at-home CRC screening tests with established high adherence are of even greater relevance (Respaut R, Nelson DJ. *Reuters*. April 27, 2020).

Results from a recent real-world study published in the *Journal of Medical Screening* determined high adherence rates were achievable with the mt-sDNA test for CRC screening in a large, fully insured Medicare population—albeit looking at data collected before the current pandemic.

Among 368,494 Medicare beneficiaries with a valid mt-sDNA test order, the overall cross-sectional adherence was 71.1%.[5] For comparison, a recent internal assessment of meta-analyses and retrospective cross-sectional data at Exact Sciences indicated that actual programmatic adherence for annual FIT likely ranges between 40-60%.[6,7,8,9,10,11]

The mt-sDNA adherence study results, which were relatively consistent regardless of age, sex, Medicare coverage type, geography, and test order date, provide a window into what can be achieved while much of the country remains sheltered in place, and as health systems and their providers work to get patients safely back into health care settings.[5]

Study authors speculate that "the noninvasive approach, widespread accessibility, and embedded patient navigation system likely contributed to successful test completion and can be further leveraged to accelerate realization of CRC screening participation targets."[5] The robustness of the screening navigation program that supports the mt-sDNA test may not be well appreciated. It includes a 24/7 patient navigation system in 240+ languages designed to support users throughout their screening journey to facilitate test completion, while also making assistance available to patients with insurance coverage questions.[12]

## Screening in the new normal

After a provider prescribes mt-sDNA, it is delivered both to and from a patient's home, limiting their interaction with the health care system at a time when limited interaction is critically important to prevent the spread of COVID-19. Additionally, patients can request the mt-sDNA test online through licensed telehealth providers and complete their part in the screening process from home.

This offers a solution for patient populations in communities where screening rates are low, whether due to geographic or systemic barriers. These factors can be leveraged to maintain CRC screening rates while other preventive health tools may be inaccessible.

## New solutions and new challenges

Regular adherence to screening with either stool-based tests or structural examinations results in a reduction in premature CRC death over a lifetime.[4] Given how challenging CRC screening can be during this unprecedented time, it is imperative that health care providers offer patients screening choices with features designed to increase adherence, including the mt-sDNA test.

Beyond logistical challenges, patients may be less willing to seek preventive care at a health care facility for some time to come—recognizing the linger-

ing anxiety or concerns for safety, especially among older populations who have been disproportionately impacted by COVID-19. Offering choice among screening modalities can provide long-term benefits for both patients and providers,[13] especially when these modalities can be requested and completed without a patient leaving their home.

> Offering choice among screening modalities can provide long-term benefits for both patients and providers, especially when these modalities can be requested and completed without a patient leaving their home.

Relatedly, it is vitally important for patients and providers to understand the need for follow-up colonoscopy after a positive stool-based screening test. If a delay in follow-up colonoscopy could cause undue anxiety for any given patient, providers may wish to discuss the pros and cons of screening for CRC at this time. While some delay may be acceptable—new 2020 NCCN guidance for CRC screening suggested follow up happen no later than six to ten months following a positive stool-based test—care must be taken to ensure the follow-up colonoscopy occurs.[14]

A pre-pandemic real-world study of over 16,000 mt-sDNA users found nearly 9 in 10 average-risk patients who received a positive mt-sDNA test followed up with a diagnostic colonoscopy.[15] In our new normal, the health care community should consider working together in new ways to facilitate greater connection along the screening continuum to ensure completion of care.

## Looking ahead

We must consider the long-term impact of COVID-19 on our health care system. As we begin to re-open health care facilities, clinicians will have to prioritize endoscopy procedures based on the level of medical urgency.

Patients with a positive stool test result who need a follow-up colonoscopy should be triaged above elective screening exams, aiding in the risk stratification and timely evaluation of screen-eligible patients. Patients with a negative result should continue participating in a screening program at an interval and with a method appropriate for the individual patient.

Although high-performing screening tests can help detect cancer earlier, the impact is negligible if patients do not, or cannot, follow through and complete the full process, including diagnostic follow-up, when indicated. By working closely together, the healthcare community can eliminate many barriers to effective CRC screening and help to ensure that patients have access to their preferred test option.

If we focus on implementing features designed to increase adherence, we can ultimately improve screening rates—a truly welcome victory in the midst of our fight against the pandemic.

**Disclosures:** Dr. Limburg serves as chief medical officer of the Screening business unit for Exact Sciences through a contracted services agreement with Mayo Clinic. Limburg and Mayo Clinic have contractual rights to receive royalties through this agreement.

Cologuard is intended for adults 45 and older at average risk for colorectal cancer. Rx only.

### References

1. *Morning Consult. American College of Emergency Physicians COVID-19. https://www.emergencyphysicians.org/globalassets/emphysicians/all-pdfs/acep-mc-covid19-april-poll-analysis.pdf Accessed April 2020.*
2. *Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30.*
3. *Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for colorectal cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2016;315:2564-2575.*
4. *Wolf A, Fontham E, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018;68:250-281.*
5. *Weiser E, Parks PD, Swartz RK, et al. Cross-sectional adherence with the multi-target stool DNA test for colorectal cancer screening: Real-world data from a large cohort of older adults. J Med Screen. 2020 Feb 13:969141320903756. Epub ahead of print.*
6. *Joseph DA, King JB, Richards TB, et al. Use of colorectal cancer screening tests by state. Prev Chronic Dis. 2018;15:E80.*
7. *Cancer Facts & Figures 2020. American Cancer Society. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2020.html. Accessed January 13, 2020.*
8. *Senore C, Basu P, Anttila A, et al. Performance of colorectal cancer screening*

*in the European Union Member States: data from the second European screening report. Gut. 2019;68(7):1232-44.*

9. *Vart G, Banzi R, Minozzi S. Comparing participation rates between immunochemical and guaiac faecal occult blood tests: a systematic review and meta-analysis. Prev Med. 2012;55(2):87-92.*
10. *Jensen CD, Corley DA, Quinn VP, Doubeni CA, Zauber AG, Lee JK, et al. Fecal Immunochemical Test Program Performance Over 4 Rounds of Annual Screening: A Retrospective Cohort Study. Ann Intern Med. 2016;164(7):456-63.*
11. *Kapidzic A, Grobbee EJ, Hol L, et al. Attendance and yield over three rounds of population-based fecal immunochemical test screening. Am J Gastroenterol. 2014;109(8):1257-64.*
12. *Comprehensive patient support. Cologuard HCP website.https://www.cologuardtest.com/hcp/coverage-and-support/specialized-support. Accessed May 18, 2020.*
13. *Inadomi JM, Vigan S, Janz NK, et al. Adherence to colorectal cancer screening: A randomized clinical trial of competing strategies. Arch Intern Med. 2012:172(7):575-582.*
14. *National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology—colorectal cancer screening. Version 1.2020. Updated April 22, 2020. https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf. Accessed May 18, 2020.*
15. *Eckmann JD, Ebner DW, Bering J, et al. Multitarget stool DNA screening in clinical practice: high positive predictive value for colorectal neoplasia regardless of exposure to previous colonoscopy. Am J Gastroenterol. 2020;115:608-615.*

CLINICAL ROUNDUP

## Keytruda fails to meet PFS, OS, in UCC trial

Keytruda in combination with chemotherapy for the first-line treatment of patients with advanced or metastatic urothelial carcinoma did not meet its pre-specified dual primary endpoints of overall survival or progression-free survival, compared with standard of care chemotherapy.

Keytruda is sponsored by Merck.

In the final analysis of the study, there was an improvement in OS and PFS for patients treated with Keytruda in combination with chemotherapy (cisplatin or carboplatin plus gemcitabine) compared to chemotherapy alone; however, these results did not meet statistical significance per the pre-specified statistical plan.

The monotherapy arm of the study was not formally tested, since superiority was not reached for OS or PFS in the Keytruda combination arm. The safety profile of Keytruda in this trial was consistent with previously reported studies, and no new safety signals were identified.

Keytruda has three FDA-approved bladder cancer indications across multiple types and stages of bladder cancer. Additionally, Merck has an extensive clinical development program in bladder cancer and is continuing to evaluate Keytruda as monotherapy and in combination with other anti-cancer therapies across several disease settings (i.e., metastatic, muscle invasive bladder cancer, and non-muscle invasive bladder cancer).

## Inherited mutation associated with higher prostate cancer risk in African Americans

Researchers at the Keck School of Medicine have identified a variant in the genome that may explain why multiple men in the same family develop the disease—and could serve as a guide for screening,

For years, researchers have known that men of African ancestry are at greater risk of developing prostate cancer with research suggesting that inherited factors may contribute to their greater risk.

Now, a new USC study published in European Urology is the first to identify an inherited genetic variant associated with higher risk of prostate cancer in men of African descent that contributes to the clustering of prostate cancer cases within families.

"About 12% of men of African ancestry carry this particular variant in the genome, which increases their risk twofold. The variant is not found in other populations," Christopher Haiman, study author and professor of preventive medicine, Keck School of Medicine of USC, said in a statement. "But it's even more common in families with a history of prostate cancer."

One in six African American men develops prostate cancer in his lifetime. African American men are 1.8 times more likely to be diagnosed with—and 2.2 times more likely to die from—prostate cancer than white men. If a black man's brother or father had prostate cancer, his risk will be even higher.

Until now, there has been no genetic mutation or biomarker doctors could look for to determine if a particular African American man was more likely to get the disease.

While a prostate specific-antigen blood test can detect prostate cancer, many of the cancers it detects may not cause harm, while treatment can cause life-altering side effects.

In the study, which is part of the RESPOND African American prostate cancer initiative, researchers looked at 9,052 prostate cancer cases among men of African ancestry. More than 23% had this specific genetic variant. The variant was strongly associated with a prostate cancer diagnosis at an earlier age, more aggressive disease, and men with a family history of prostate cancer. In fact, 32% of the men with prostate cancer who had a family history of the disease carried the variant.

This new information may eventually help clinicians identify men who could benefit from early prostate cancer screening and treatment.

"A man of African ancestry comes in and says, 'Well, I have prostate cancer and I have a family history of the disease. Why?' Well, now there's a variant you can test to see if they and their family members carry it," Haiman said. "This is a marker that down the road may be used to identify African-Americans and their family members who are at high risk and would benefit from more precise, targeted, and earlier PSA screening."

Researchers believe this variant is one of the reasons why African American men are more likely to get prostate cancer and hope to find out more about the role genetic mutations play in their overall risk.

## Many hospitalized people with advanced cancer struggle with daily tasks

New research from Mass General Cancer Center, published in *JNCCN—Journal of the National Comprehensive Cancer Network*, found 40.2% of hospitalized patients with advanced, incurable cancer were functionally impaired at the time of admission, meaning they needed assistance with activities of daily living like walking, bathing, getting dressed, or other routine tasks.

Patients with functional impairment also had higher rates of pain, depression, and anxiety, and were more likely to have longer hospital stays and worse survival.

"Interventions addressing patients' functional impairment and symptom management could help enhance care delivery and outcomes for the highly symptomatic population of hospitalized patients with advanced cancer," lead researcher Daniel E. Lage, of Mass General Cancer Center, said in a statement. "This highlights the need for efforts to integrate functional assessments into the care of these patients to identify individuals who may benefit from physical therapy, palliative care, and/or other supportive services earlier in their hospital stay. Our finding that individuals with functional impairment experience worse survival could also help guide conversations about goals of care and hospice planning among hospitalized patients with cancer."

"We are also actively exploring interventions to help patients transition from the inpatient to the outpatient setting, which we have identified as a key challenge for patients with functional impairment," senior researcher Ryan D. Nipp, of Mass General Cancer Center, said in a statement.

The researchers studied 970 patients ages 18-and-older with advanced cancer—defined as those not being treated with curative intent—who experienced an unplanned hospital admission at Mass General Cancer Center between Sept. 2, 2014 and March 31, 2016. They measured functional impairment using nursing documentation collected at intake and stored in electronic health records, and also collected self-completed questionnaires from the patients. ADL impairment was defined as any need for assistance by another person. Overall, 390 patients (40.2%) had at least one ADL impairment with 14.8% having one or two, and 25.4% experiencing at least three areas of difficulty with daily tasks.

"Lage and colleagues highlight the important, often-missed, opportunity to routinely use hospitalization as a trigger for a careful assessment of symptoms and functional status," Toby Campbell, MD, Chief of Palliative Care at the University of Wisconsin Carbone Cancer Center, and a member of the NCCN Guidelines Panel for Palliative Care, said in a statement.

"An unplanned hospitalization for an advanced cancer patient is a watershed moment and predicts higher symptoms and shorter survival in patients with and without impaired function. Hospitalization is a crucial opportunity to facilitate critical serious illness care, including comprehensive palliative care and advanced care planning, with the promise of improving the lives of our patients," Campbell said.

## NIH scientists develop blood test to help improve HCC screening

Scientists have developed a new test that can help identify people who are likely to develop hepatocellular carcinoma. The approach uses a simple blood test to check for the patient's previous exposure to certain viruses.

A study of the new approach was led by researchers at NCI. The study also involved researchers from the National Institute of Diabetes and Digestive and Kidney Diseases and several academic centers. The findings were published June 10 in *Cell*.

"Together with existing screening tests, the new test could play an important role in screening people who are at risk for developing HCC. It could help doctors find and treat HCC early. The method is relatively simple and inexpensive, and it only requires a small blood sample," study's leader Xin Wei Wang, co-leader of the NCI Center for Cancer Research Liver Cancer Program, said in a statement

Certain factors increase a person's chances of developing HCC, such as infection with hepatitis B or hepatitis C virus or cirrhosis of the liver. People who have risk factors are recommended to get screened for HCC every six months with an ultrasound with or without a blood test for alpha-fetoprotein.

But not everyone with risk factors for HCC will develop the disease. Although screening can lead to earlier detection, most patients are diagnosed when the cancer is advanced and often incurable. However, HCC that is caught early has a much better chance of being cured.

"We need a better way to identify people who have the highest risk for HCC and who should get screened more frequently," said Wang, who is also part of NCI's Translational Liver Cancer Consortium.

"A main focus of the NCI CCR Liver Cancer Program is to develop new methods for early detection, diagnosis, and treatment, with the goal of improving outcomes for patients with HCC," Tim Greten, co-leader of the Liver Cancer Program and a collaborator of the study, said in a statement

Many screening tests detect features of cancer cells. But those features can change over time, and not all cancer cells in a tumor have the same characteristics. The NCI team took a different approach: detecting features of the cancer's environment rather than cancer cells themselves.

More research is providing evidence that cancer development is influenced by interactions between viruses and the immune system. The team reasoned that certain interactions between viruses and the immune system may raise the risk of developing HCC.

To explore that possibility, the scientists scanned people's blood for "footprints" left behind by past viral infections. Because these footprints are left in antibodies, proteins made by the immune system, they also reflect how the immune system reacted to the infection. The mixture of footprints each person has creates a unique pattern, which the researchers called a viral exposure signature.

The team checked for the footprints of more than 1,000 different viruses in blood samples from around 900 people, including 150 who had HCC. They identified a specific viral exposure signature that could accurately distinguish people with HCC from people with chronic liver disease and healthy volunteers. This signature contained footprints from 61 different viruses.

The researchers then tested the signature on blood samples from 173 people with chronic liver disease who were part of a 20-year study. During that time, 44 of the participants developed HCC. Using blood samples taken when the cancer was diagnosed, the signature correctly identified those who developed HCC (area under the curve, AUC=0.98). Importantly, the signature also worked when the researchers used blood samples taken at the beginning of the study, up to 10 years before diagnosis (AUC=0.91).

The signature appeared to be far more accurate than an alpha-fetoprotein test (AUC=0.91 vs. 0.62). An AUC of 0.5 indicates that a test is no better than chance in identifying disease, whereas an AUC of 1.0 represents a test with perfect accuracy.

The scientists are continuing to study their approach and plan to test it in clinical trials. They are collaborating with Katherine McGlynn, Ph.D., of NCI's Division of Cancer Epidemiology and Genetics to test the approach in a prospective surveillance study of people with risk factors for HCC.

It's possible that viral infections—even ones that don't cause cancer—may change the immune system in ways that influence the development of other cancers. For example, certain infections may lessen the immune system's ability to keep cancer cells in check. NCI scientists are testing the viral exposure signature in a study of prostate cancer, and others are considering applying the approach to a screening study for ovarian, esophageal, liver, and breast cancer in Africa.

## Yale scientists develop experimental method to study infection and disease, including COVID-19

Yale Cancer Center scientists have developed a cell screening method for agents that alter biologic functions. This approach uses thousands of artificial proteins called "traptamers" and may help to answer research questions that are difficult to address with other cell screening methods, including the SARS-CoV-2 virus, COVID-19.

The data was published in *Cell Reports*.

"The traptamer screening approach identifies a molecular target required for human papillomavirus infection," lead author Daniel DiMaio, deputy director of YCC, professor of genetics, molecular biophysics and biochemistry, and therapeutic radiology, said in a statement.

Traptamers are extremely short proteins designed to bind to transmembrane proteins. DiMaio's lab developed the technology more than a decade ago, based on its discoveries about a bovine papillomavirus gene called E5, which provides a model for traptamer design.

In traptamer screening, researchers first generate many versions of the artificial proteins, each one being unique. The scientists then screen these artificial proteins for activity in a large number of cells. Any traptamer that binds to a cell transmembrane protein may activate or inactivate it, and thus can affect processes controlled by the protein.

Over the years, DiMaio and his collaborators have isolated traptamers tailored for specific transmembrane proteins that are crucial to cellular function, such as infection by HIV. More recently, DiMaio and his team wondered if traptamers could be used as a screening tool to block a process such as HPV infection, another main line of research in his lab, without designating a specific transmembrane protein beforehand.

To test this idea, the Yale team generated about 250,000 traptamers, expressed them in HeLa human cells, and added HPV. Researchers engineered a form of HPV expressing a gene that can stop the cells from growing, providing a selection for traptamers that block infection.

The screen allowed them to isolate a traptamer that inhibits a cellular protein called TBC1D5, thereby blocking HPV infection. Follow-up research demonstrated that TBC1D5 regulates a protein called Rab7, a key player in a biological pathway by which HPV enters cells. These findings in turn suggested that Rab7 may be a likely target for anti-HPV therapies.

DiMaio noted that HPV vaccines, which are effective and safe, are the first line of

defense against the virus. Unfortunately, not everyone can or will be vaccinated, and there's still a need for other treatments to defend against HPV or slow its spread.

Traptamer screening may also be a powerful tool to investigate other diseases. For instance, Jian Xie, a postdoctoral researcher in the DiMaio lab and the first author of the paper, has designed traptamer screens against the SARS-CoV-2 virus, in collaboration with Craig Wilen, assistant professor of laboratory medicine and immunobiology.

DiMaio says that the method may offer advantages over screening based on a widely adopted DNA-editing technology called CRISPR. In CRISPR screens, which have fueled many major recent advances in research, scientists "knock out" different single genes in a population of cells, which prevents the genes from expressing proteins, to see how that alters a given biological process.

Yale's Erin Heim and Mac Crite are co-authors of the paper. Lead funding came from NCI and the National Institute of Allergy and Infectious Diseases.

DRUGS & TARGETS

# Nivolumab approved by FDA for esophageal squamous cell carcinoma

Opdivo (nivolumab) was approved by FDA for patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based chemotherapy.

Efficacy was investigated in ATTRACTION-3 (NCT02569242), a multicenter, randomized (1:1), active-controlled, open-label trial in 419 patients with unresectable advanced, recurrent, or metastatic ESCC. Patients who were refractory or intolerant to at least one fluoropyrimidine- and platinum-based regimen received nivolumab 240 mg by intravenous infusion over 30 minutes every 2 weeks (n=210), or investigator's choice of taxane chemotherapy consisting of docetaxel (75 mg/m2 intravenously every 3 weeks) or paclitaxel (100 mg/m2 intravenously once a week for 6 weeks followed by 1 week off) (n=209).

The major efficacy outcome measure was overall survival. Additional efficacy outcome measures were overall response rate, response duration, and progression-free survival as assessed by the investigator using RECIST 1.1.

The trial demonstrated a statistically significant improvement in OS. Median OS for patients receiving nivolumab was 10.9 months (95% CI: 9.2, 13.3) compared with 8.4 months (95% CI: 7.2, 9.9) for patients receiving investigator's choice of taxane chemotherapy (HR: 0.77; 95% CI: 0.62, 0.96; p=0.0189). OS benefit was observed regardless of tumor PD-L1 expression level. The ORR was 19.3% (95% CI: 13.7, 26) in the nivolumab arm versus 21.5% (95% CI: 15.4, 28.8) in the taxane chemotherapy arm, with median response duration of 6.9 months (95% CI: 5.4, 11.1) and 3.9 months (95% CI: 2.8, 4.2), respectively. The trial did not demonstrate an improvement in PFS (HR: 1.1; 95% CI: 0.9, 1.3).

# Supportive care biosimilar Nyvepria approved by FDA

Nyvepria (pegfilgrastim-apgf), a biosimilar to Neulasta (pegfilgrastim), received FDA approval.

Nyvepria is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

Nyvepria is sponsored by Pfizer.

The FDA approval was based on the review of a comprehensive data package and totality of evidence demonstrating a high degree of similarity of NYVEPRIA to its reference product.

# Berubicin receives FDA Orphan Drug status for gliomas

Berubicin was granted Orphan Drug Designation by FDA for the treatment of malignant gliomas.

Berubicin is sponsored by CNS Pharmaceuticals Inc.

In the phase I trial of Berubicin to treat glioblastoma under a prior developer, 44% of the patients demonstrated a significant improvement in progression-free survival, and one patient experienced a complete response.

# The Cancer Letter receives investigative, design awards

*The Cancer Letter* received five 2020 Dateline Awards from the Washington, D.C. Chapter of the Society of Professional Journalists:

- Art/Photo Illustration, Newsletter/Trade Publications, first place, by Katie Goldberg, for illustrations of the 2019 ASCO annual meeting
- Editorial Cartooning, Newsletter/Trade Publications, first place, by Katie Goldberg
- Infographic, Newsletter/Trade Publications, first place, by Jacqueline Ong
- Art/Photo Illustration, Newsletter/Trade Publications, finalist, by Katie Goldberg, for cover art of 2019
- Investigative Journalism, Newsletter/Trade Publications, finalist, for "Thirty Days to Death by Cancer," by Matthew Ong and Paul Goldberg

This is the third consecutive year *The Cancer Letter* has won first-place design awards, and the first year *The Cancer Letter* has won awards for cartooning and infographics.

This is also the fourth award Ong has received from SPJDC for his series on cancer-related surgical outcomes, minimally invasive surgery, FDA regulation of devices, and new surgical techniques for the prevention or treatment of cancer.

Here are a few of *The Cancer Letter*'s award-winning covers, cartoons, and infographics published in 2019: