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American Association for Cancer Research®

AACR REPORT ON THE IMPACT OF COVID-19 ON CANCER RESEARCH AND PATIENT CARE

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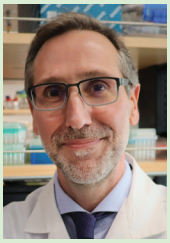

Antoni Ribas, MD, PhD, FAACR
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Chair, *AACR Report on the Impact of COVID-19 on Cancer Research and Patient Care* Steering Committee
Chair, AACR Task Force on COVID-19 and Cancer

Margaret Foti, PhD, MD (hc)
AACR Chief Executive Officer

On behalf of the Steering Committee for the *AACR Report on the Impact of COVID-19 on Cancer Research and Patient Care*

This is an uncertain time for everyone around the world, including those of us working in the field of cancer science and medicine and the patients and families who rely on us. In the United States and globally, there has been remarkable progress against cancer over the past few decades. However, our ability to continue the current pace of progress is in jeopardy because of the enormous global public health challenge posed by Coronavirus Disease 2019 (COVID-19). Because of their expertise in viral biology, immunology, mRNA vaccines, and therapeutic development, cancer researchers and physicians around the world have been deployed to the front lines of the COVID-19 pandemic to help mitigate this scourge that has already caused over 289 million cases and over 5.4 million deaths globally. The *AACR Report on the Impact of COVID-19 on Cancer Research and Patient Care* presents current evidence on the burden of COVID-19 among patients with cancer and highlights the challenges as well as future opportunities created by the pandemic in cancer research and patient care.

Patients with cancer have been especially vulnerable to COVID-19. Those with hematologic cancers as well as patients receiving B cell-targeted therapeutics are not only at a markedly higher risk for COVID-19, but also have shown poor responses to the available vaccines. There are grave concerns among public health experts that the delays in cancer screening, diagnosis, and treatment caused by the pandemic will have significant negative effects on outcomes for patients. There are particularly serious concerns for racial and ethnic minorities and other medically underserved populations because these groups already experience cancer health disparities and have shouldered a disproportionate burden of COVID-19. The stark disparities in the burden of COVID-19 have refocused the nation's attention on the inequities in health care, and it is critical that everyone play a role in eradicating the social injustices that are barriers to health equity.

All stakeholders in the medical research community have come together and responded in innovative ways to continue cancer research and patient care despite the severe disruptions caused by COVID-19. Remarkable changes in the conduct of clinical trials have been implemented, many of which should persist beyond the pandemic. The changes are designed to ensure a patient-centric approach and to enhance patient safety and experience while improving clinical trial efficiency and outcomes. Some of the changes have the potential to improve long-standing challenges in clinical research, by enhancing enrollment of patients in cancer clinical trials overall, as well as by increasing participation from racial and ethnic minorities and other medically underserved populations. Another opportunity in patient care that has been brought into focus during the pandemic is telemedicine. According to some practicing oncologists, the equivalent of decades of progress in facilitating the implementation, uptake, and access of telehealth has been made in months. These adaptations were driven largely by necessity and the commitment from all stakeholders in the medical research community to safely continue patient care during the pandemic. Moving forward, it will be critical to maintain and facilitate access so that telehealth care can be delivered equitably to all patients.

While we have witnessed unprecedented global collaborations and unparalleled progress in the face of a global pandemic, the past two years have also presented unique challenges to the medical research community. As one example, there has been a rapid proliferation of scientific and medical misinformation. Misinformation can bring serious harm to patients, communities, and populations. The medical research community must combat misinformation through increased public education and awareness. It is also important to explain that scientific evidence evolves over time as new data become available. Another challenge brought on by the pandemic is its multifaceted adverse impact on the cancer research and care workforce, especially on early-stage investigators, women, and underrepresented minorities. According to a recent AACR survey, nearly 100 percent of the respondents reported severe interruptions in their research and career advancements during the past two years.

With profound thanks to the entire cancer community, AACR has remained steadfast in its mission of preventing and curing

all cancers through high-quality research, dissemination of scientific knowledge, public education, and science policy throughout the pandemic. Combating the pandemic head-on, AACR brought together some of the greatest scientific minds at the first-ever conference on COVID-19 and cancer in July 2020 and a follow-up conference in February 2021 to discuss the rapidly emerging data in basic, clinical, and epidemiologic research related to COVID-19 and cancer. Mobilizing our membership, AACR created a special COVID-19 and Cancer Task Force and hosted patient advocate forums to identify barriers and develop solutions to optimizing cancer care during the crisis. By pioneering scientific conferences, publishing groundbreaking science and policy articles, many of which were inspired by the Task Force, and funding meritorious cancer research, AACR has proudly catalyzed the advancement of research on COVID-19 and cancer during these tumultuous times.

It is imperative that cancer researchers continue to contribute their unique expertise to combat the ongoing challenges of COVID-19. However, we must also keep in the forefront of our minds that there are many patients with cancer who are urgently awaiting more effective treatment options. Ensuring that medical research remains a priority for our nation's policy makers is essential if we are to reestablish the momentum against cancer, revitalize the economy, and help the United States to maintain its position as the global leader in science and medicine. Therefore, the AACR urges Congress to continue to invest in medical research and the health care workforce, expand access to quality health care that includes telehealth, strengthen and modernize cancer clinical trials, and rebuild the U.S. public health infrastructure to better prepare us for any pandemics that may arise in the future. These actions will ensure that we continue on the path of accelerating lifesaving progress for patients with cancer around the world.

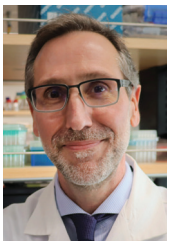
ABOUT THE AMERICAN ASSOCIATION FOR CANCER RESEARCH

Founded in 1907, the American Association for Cancer Research (AACR) is the world's first and largest professional organization dedicated to advancing cancer research and its mission to prevent and cure cancer. AACR membership includes 49,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and patient advocates residing in 126 countries. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, diagnosis, and treatment of cancer by annually convening more than 30 conferences and educational workshops—the largest of which is the AACR Annual Meeting, with more than 74,000 attendees for the 2020 virtual meetings and more than 22,500 attendees for past in-person meetings. In addition, the AACR publishes 10 prestigious, peer-reviewed scientific journals and a magazine for cancer survivors, patients, and their caregivers. The AACR funds meritorious research directly as well as in cooperation with numerous cancer organizations. As the Scientific Partner of Stand Up To Cancer, the AACR provides expert peer review, grants administration, and scientific oversight of team science and individual investigator grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and other policymakers about the value of cancer research and related biomedical science in saving lives from cancer. For more information about the AACR, visit **AACR.org**.

EXECUTIVE SUMMARY

The Coronavirus Disease 2019 (COVID-19) pandemic has disrupted the everyday lives of billions of people, exhausted the health care infrastructure and workforce, upended societal norms, and shattered economies worldwide.

Since the onset of the pandemic in December 2019, one in six Americans has been diagnosed with the disease and nearly one million people in the U.S. have died from it. The damaging impact of the pandemic on the lives of older adults, racial and ethnic minorities and other medically underserved populations, and individuals with certain preexisting conditions, such as patients with cancer, has been disproportionately high and multifaceted.



"We have tackled cancer in a science-based manner, where we define the problem, understand the processes, and then develop treatments or ways to improve health. The same had to be done for COVID-19. Cancer research community had generated so many tools to study the cancer—sequencing; developing antibodies; pioneering targeted therapies—that helped researchers address COVID-19. And the best example of all is the COVID-19 mRNA vaccines."

Antoni Ribas, MD, PhD, FAACR
AACR President, 2020-2021
Chair, *AACR Report on the Impact of COVID-19 on Cancer Research and Patient Care* Steering Committee
Chair, AACR Task Force on COVID-19 and Cancer

As the first and largest professional organization in the world with a steadfast mission to prevent and cure all cancers, the American Association for Cancer Research (AACR) is dedicated to increasing public understanding of cancer and the important role of medical research in saving lives. The *AACR Report on the Impact of COVID-19 on Cancer Research and Patient Care* is one of AACR's several initiatives to fully understand and mitigate the pandemic's impact on the cancer research and care continuum and describes the many ways by which COVID-19 has affected cancer science and medicine. This report highlights how cancer researchers responded to the significant challenges posed by COVID-19 and documents lessons learned from the pandemic that can be implemented to accelerate advances in cancer research and markedly improve patient care in the future. The impact of the pandemic on patients with cancer is underscored through compelling personal experiences of the courageous individuals who shared their stories with AACR.

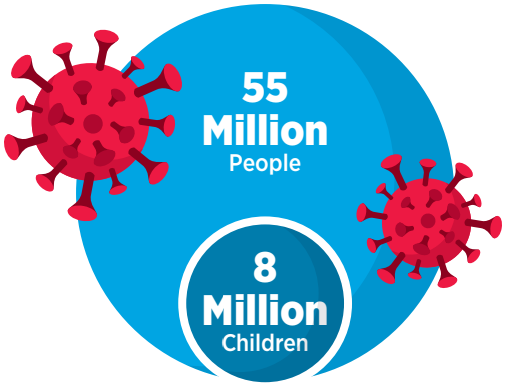
AACR is committed to advocating for increased annual federal funding to government entities that drive progress against cancer and improve public health, in particular, the National Institutes of Health (NIH), National Cancer Institute (NCI), U.S. Food and Drug Administration (FDA), and Centers for Disease Control and Prevention (CDC). This report underscores the urgent and critical need for additional funding for medical research to alleviate the negative effects of the pandemic on cancer science and medicine and to maintain positive momentum against cancer.

UNDERSTANDING THE COVID-19 PANDEMIC

COVID-19 was first reported in December 2019 in Wuhan, China, as pneumonia with unknown origins. Soon after, a novel coronavirus—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—was identified as the cause, and the disease was designated COVID-19 and declared a pandemic by the World Health Organization (WHO). Since then, the toll of the pandemic has been devastating, with more than 5.4 million deaths and more than 289 million cases worldwide and the largest drop in life expectancy since World War II in just over two years.

SARS-CoV-2 belongs to a large family of coronaviruses that are mostly found in birds and small mammals but have occasionally been known to infect humans, including three that have been responsible for the deadly global outbreaks of

COVID-19 DIAGNOSES IN THE UNITED STATES AS OF JANUARY 1, 2022



Nearly one million people have died from the disease.

severe acute respiratory syndrome (SARS) in 2002-2004, Middle East respiratory syndrome (MERS) in 2012, and COVID-19. Many variants of SARS-CoV-2 including the most recent and rapidly spreading Omicron, have emerged since the onset of COVID-19. SARS-CoV-2 infects by attaching to the ACE2 protein that is found on the surface of certain human cells in the nasal passages, lungs, and gastrointestinal tract, among other organs. This may explain the vast array of symptoms that are experienced by patients with COVID-19, but the exact mechanism(s) by which the virus affects multiple organs is an area of active research.

COVID-19 predominantly spreads when an infected person coughs, sneezes, or talks, releasing droplets that contain the virus into the air, which infect nearby individuals who are in close contact with the infected person. Severe COVID-19 causes pneumonia and acute respiratory distress syndrome (ARDS), which are associated with difficulty in breathing and low blood oxygen levels. If unchecked, ARDS can progress to respiratory failure, which is the cause of death in many fatal cases.

The immune system plays a crucial role in fighting COVID-19 infection by releasing antibodies that restrict the ability of SARS-CoV-2 to infect cells, as well as by killing any cells that have already been infected by the virus. Thus, individuals with weakened or compromised immune systems—older adults and individuals of any age with certain underlying medical conditions including cancer, such as **Julie Campbell** (see p. 46) and **Rachel Orth** (see p. 66)—are at an increased risk for severe COVID-19 illness. Beyond underlying health conditions, modifiable risk factors such as obesity and smoking, which are also linked to diagnoses of cancer, increase the risk for severe COVID-19.

Individuals from racial and ethnic minorities and other medically underserved populations are disproportionately shouldering the burden of the pandemic because of many of the same structural and systemic inequities that cause cancer health disparities. It is pivotal that all stakeholders come together to address these injustices and ensure that all segments of the U.S. population have equitable access to quality health care.

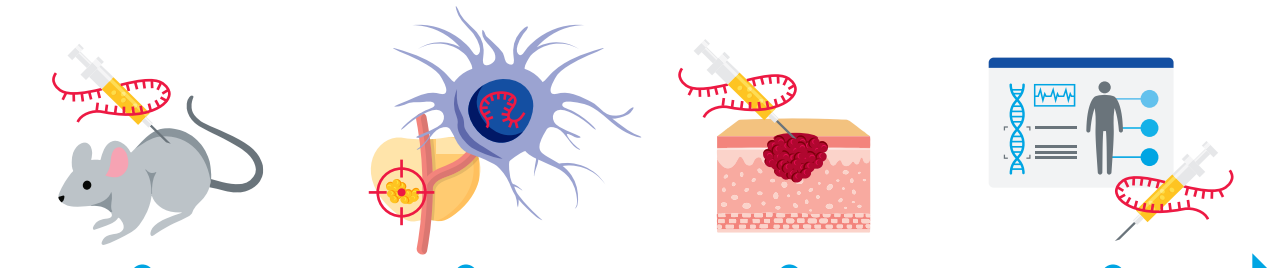
FDA has approved or authorized three vaccines against COVID-19. COVID-19 vaccines are currently widely available for all individuals age 5 and older, and 63 percent of the U.S. population has been fully vaccinated as of January 2022. The vaccines are safe and effective and reduce the risk of severe illness from COVID-19. In addition, FDA has approved or authorized several treatments for the management of patients with COVID-19, and there are numerous additional agents that are being evaluated in clinical studies.

CANCER RESEARCHERS WORKING TO COMBAT THE COVID-19 PANDEMIC

Decades of investment in cutting-edge cancer research have led to major breakthroughs against cancer and have uniquely positioned cancer scientists to respond to the many challenges posed by COVID-19. Many cancer researchers and physicians provided their extensive expertise in genetics, immunology, and drug development to investigate COVID-19 biology and assist in developing vaccines and therapeutics. For example, NCI unified its national network of serology centers, initially established to standardize human papillomavirus antibody testing, and created the Serological Sciences Network to support research on SARS-CoV-2 immunology and to increase the nation's serological testing capacity. Research from this network has uncovered important insights into the mechanisms of immune response to COVID-19. Similarly, decades of research into mRNA vaccines and cancer immunotherapy paved the way for the development of SARS-CoV-2 vaccines at an unprecedented speed. Researchers have also drawn knowledge from cancer biology to investigate the mechanism by which SARS-CoV-2 enters the host cell and the immune response to COVID-19.

The tremendous success of the COVID-19 vaccines has renewed enthusiasm for mRNA-based cancer immunotherapies,

SELECTED EXAMPLES OF mRNA VACCINE RESEARCH IN CANCER



1995
mRNA tested as a cancer vaccine in mice

2002
First clinical trial conducted using immune cells containing mRNA against prostate cancer

2009
Direct injection of mRNA tested for melanoma treatment

2017
First human testing of personalized mRNA cancer vaccines began by Moderna

and many cancer scientists believe that the next wave of breakthroughs in mRNA technologies will revolutionize the landscape of cancer vaccines.

CANCER IN THE MIDST OF COVID-19 AND BEYOND

COVID-19 has interrupted all aspects of the cancer research and care continuum. Certain patients with cancer, who have a weakened immune system because of their cancer and/or the treatment, are at a significantly higher risk of COVID-19 infection and severe disease. Among patients with cancer, individuals with hematologic malignancies such as **Larry Saltzman, MD** (see p. 52), patients with lung cancer, and those on active anticancer treatments are especially vulnerable. Based on current knowledge, the most significant treatment-related risk factors are certain drugs that alter the function of normal B cells, which make infection-fighting antibodies. Examples of such drugs include immunotherapies such as CAR T cells; molecularly targeted therapies directed against proteins, such as CD20, found on the surface of B cells; inhibitors of proteins important for B-cell function; and corticosteroids.

COVID-19 vaccines are effective in most patients with cancer, with few to no side effects. With a wider availability of highly effective vaccines against COVID-19, getting vaccinated is the first line of defense against SARS-CoV-2 infection. Findings from a large study showed that patients with cancer had a 58 percent less chance of SARS-CoV-2 infection after receiving the second dose of one of the mRNA vaccines against COVID-19. However, it is important to note that patients with certain types of blood cancers and/or those receiving specific types of anticancer treatments respond to the vaccines to a lesser extent and remain vulnerable to SARS-CoV-2 infections and complications from COVID-19. These patients should exercise additional care and discuss with their health care provider teams the best time to get vaccinated during their experience with cancer and whether additional doses are beneficial. In addition, CDC recommends that patients with cancer continue to exercise all preventive measures, including wearing a mask, social distancing, frequently washing hands, avoiding crowded gatherings, and minimizing nonessential travel. A close consultation with a health care provider team is also an effective way for patients with cancer, their caregivers, and survivors of cancer to avoid COVID-19-related misinformation.

79 percent of patients with solid tumors had antibodies against SARS-CoV-2 six months after receiving the second dose of the BNT162b2 vaccine (Comirnaty, Pfizer-BioNTech) compared to 84 percent of healthy individuals.

In the United States in 2020, the **risk of COVID-19** infection was **seven times higher in patients diagnosed with cancer** compared to those with no history of cancer. Notably, **Black patients with breast or prostate cancer** were at **more than five times higher risk of COVID-19** infection compared to individuals who are white.

The pandemic has caused serious interruptions across the cancer care continuum. Preventive measures to contain the pandemic, as well as the reduced access to health care systems overwhelmed by patients with COVID-19, have resulted in a sharp decline in cancer screening. For example, there was an 87 percent decline in breast cancer screening in April 2020 compared to the average for the same month over the previous five years. Following delayed cancer screening, many individuals, such as **Wenora Johnson** (see p. 60) and **Senator Amy Klobuchar** (see p. 80), are being diagnosed with precancerous lesions and early-stage cancers that could have been detected sooner if their routine cancer screenings had taken place as usually scheduled. Experts fear that missed cancer screenings during the pandemic will potentially lead to an increase in advanced-stage cancer diagnoses in the coming years and may result in an increase in cancer-related mortality. Effective strategies to raise awareness of the importance of preventive health care are critical to alleviate the potential impact of delayed screening on cancer-related health outcomes.

> **"While the world's attention may have shifted to the pandemic, the challenges of cancer have not subsided. Support for cancer research and cancer clinical care is more critical than ever."**
>
> **Sharon Gorski, PhD**
> **Distinguished Scientist, BC Cancer Research Institute, Canada**
> 2017 Neuroendocrine Tumor Research Foundation–AACR Grant Recipient

The pandemic also resulted in modified treatment regimens for many patients with cancer, such as **Federico de Armas Heinzen** (see p. 64) and **Julie Campbell** (see p. 46), who were unable to travel to health care facilities because of the preventive measures necessitated by the pandemic. Others had to delay or postpone their cancer treatment. Furthermore, evidence is accruing that the mental and physical health of patients with cancer, their caregivers, and cancer survivors was negatively affected by pandemic-related social isolation and financial stress, as well as by concerns about timely access to cancer treatments and disease recurrence or cancellation of cancer treatments. These concerns are heightened among adolescent and young adult patients with cancer, such as **Rachel Orth** (see p. 66) and **Allyson Pile** (see p. 68), who face a

unique set of challenges from cancer diagnosis and treatment, including long-term cancer care along with prolonged monitoring for disease recurrence or long-term complications from cancer treatments.

There are also concerns that the pandemic may exacerbate cancer health disparities. All stakeholders must make concerted efforts to learn from and address disparities exposed by the COVID-19 pandemic and use this knowledge to eliminate all health disparities, including disparities experienced by patients with cancer. As the cancer research community recovers from the COVID-19 pandemic, it is more important than ever to invest in cancer health disparities research, which includes community outreach, education, and engagement efforts.

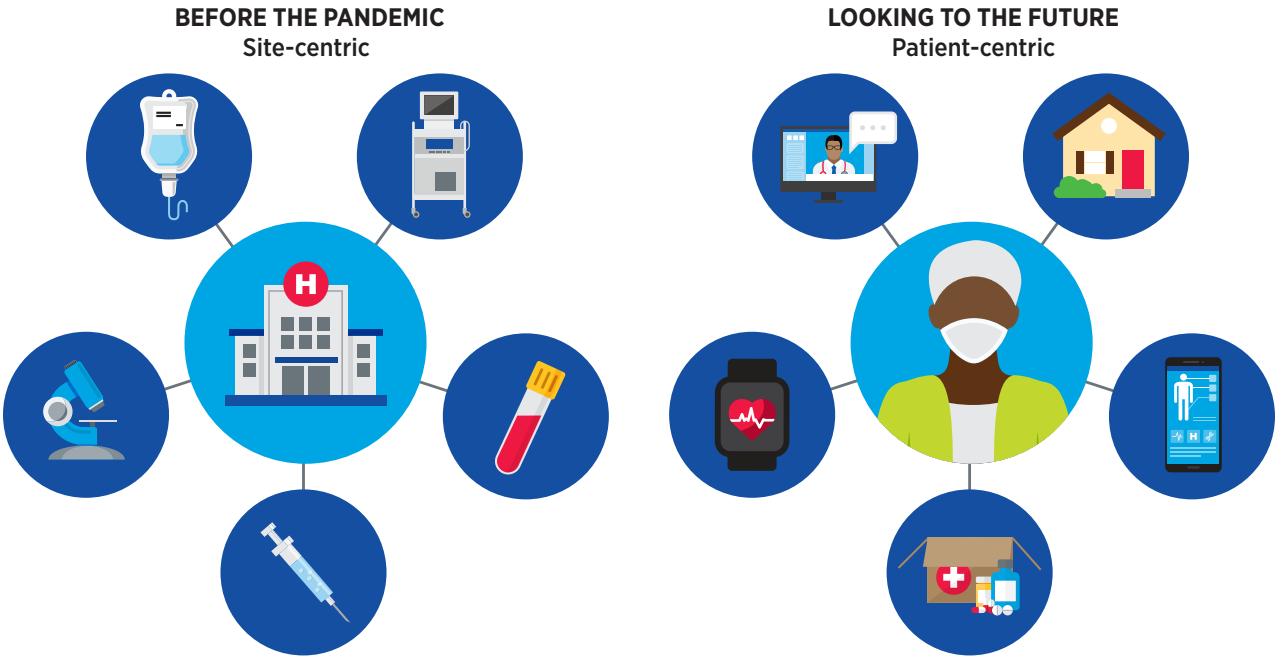
> **"The shutdown of our laboratory led to delays in multiple large experiments, both in terms of execution and supply chain and labor shortages. As a mother of an infant during COVID-19, I had additional challenges as I struggled to care for my child while writing career development awards and manuscripts. This slowed submission processes, which has delayed my career development."**
>
> **Lillian Guenther, MD**
> **Instructor, Harvard Medical School, Boston, Massachusetts**
> 2018 QuadW Foundation-AACR Fellowship for Clinical/Translational Sarcoma Research Recipient

COVID-19 led to closures of research laboratories; interrupted clinical trials; negatively impacted career development opportunities for the science, technology, engineering, and mathematics (STEM) workforce, especially for women and minority early-stage investigators; and caused substantial burnout among health care workers. A recent AACR survey of cancer researchers found that 87 percent of the respondents experienced lost productivity and 61 percent indicated that they missed career advancement opportunities due to the pandemic. Another concerning aspect is the limited availability or lack of job opportunities for early-stage investigators as academic institutions face unprecedented financial challenges because of the pandemic. There is an urgent need for the necessary funding, mentorship, and support to prevent talented scientists from exiting the cancer workforce and to maintain the momentum of impressive progress against cancer.

FUTURE OF CANCER SCIENCE AND MEDICINE BEYOND COVID-19

Despite many adverse effects of the pandemic on the cancer care continuum, some of the lessons learned from COVID-19 have the potential to help improve cancer research and patient care as we recover from this extraordinary public health crisis. The necessary preventive measures to halt the spread of COVID-19 accelerated the adoption of telemedicine—the delivery of health care from a distance using electronic information and technology, such as computers and the Internet—across the cancer care continuum. In July 2021, the use of telemedicine for health care needs was 38 times higher than before the pandemic. A nationwide poll revealed that most Americans welcomed the expansion of telehealth, and 43 percent of the telehealth users

REDESIGNING THE CANCER CLINICAL TRIALS



said they want to continue using telehealth services after the pandemic has ended. Moving forward, implementing telehealth for the routine care needs of patients with cancer offers a blueprint for broader and more permanent implementation of telemedicine, with the potential to reduce physician burnout and improve patient care.

The pandemic also necessitated changes to the conduct of clinical trials—such as the use of electronic consent to clinical trial participation and the shipment of experimental anticancer therapeutics to patients' residences—to ensure the continuity of lifesaving clinical studies. The regulatory changes to the design of clinical trials offer a path forward for patient care that is patient-focused and have the potential to increase patient participation and minimize the time it takes to safely test anticancer therapeutics. These adaptations can also minimize the financial burdens (e.g., cost of travel to the health care facility) and logistical burdens (e.g., taking time off from work to go to a health care facility) on clinical trial participants.

The pandemic has also resulted in modifications to cancer treatment regimens, such as increased time between doses or the use of oral instead of intravenous route of administration. Long-term studies will be important to determine whether such changes improve overall patient survival.

Worldwide scientific collaborations and rapid sharing of resources and expertise, already staples of the team science approach in cancer science and medicine, also offer a framework for rapidly responding to any future public health crises of this magnitude.

POLICIES TO COMBAT THE IMPACT OF A GLOBAL HEALTH CRISIS ON CANCER SCIENCE AND MEDICINE

The COVID-19 pandemic challenged the medical research community in many ways, including through the loss of productivity because of the suspension of laboratory activities and delays in reporting results of ongoing basic and clinical research. These issues cost NIH and its grantees approximately $16 billion in research costs. NIH took many important steps to assist researchers during these challenging times, such as extending deadlines for applications, allowing delayed submission of preliminary data after grant deadlines, authorizing grants to cover salaries and stipends of scientists during laboratory closures, and extending project timelines and requirements. NIH and NCI also provided flexibility with timelines and funding, such as no-cost extensions, case-by-case administrative supplements for unanticipated costs, and extensions on some grants due to delays caused by COVID-19. However, additional funding is needed to defray the costs incurred by the pandemic and revitalize the medical research enterprise.

The COVID-19 pandemic greatly interrupted the conduct of cancer clinical trials by exacerbating existing hurdles for trial participation. In response, FDA outlined voluntary flexibilities that include using telemedicine to assess outcomes and wellness; home delivery of trial medications; remote consenting; and collaborations with local clinics, imaging facilities, and laboratories. If implemented permanently, these changes could decrease costs and make participation in cancer clinical trials more equitable for all populations including those belonging to racial and ethnic minorities and other medically underserved groups.

The federally declared public health emergency in response to the COVID-19 pandemic resulted in unprecedented, rapid shifts to support flexible telehealth use for both health care providers and the patients they serve. Multiple policies and legislations enacted in response to the pandemic allowed insurance coverage of telehealth visits and permitted providers to expand telehealth delivery to patients across state lines if permissible by the state, serve new and established patients remotely, and supervise patients using either audio or video communication.

It will be vitally important to rebuild the health care infrastructure, modernize health reporting systems, retain and train the health care workforce, and combat health-related misinformation while building public confidence in health care systems before any future pandemics. To do so and to minimize interruptions in cancer science and medicine during any future public health crises, it is pivotal for Congress to authorize robust, sustained, and predictable investments in public health and medical research.

THE AACR CALL TO ACTION

Decades of investment in basic, translational, and clinical research have enabled scientists to develop COVID-19 diagnostics, treatments, and vaccines at a pace never seen before, as highlighted by **Senator Roy Blunt** (see p. 78). This robust approach to medical research has saved hundreds of thousands of lives from COVID-19 in the United States and increased protection for patients with cancer who are immunocompromised and are at a significant risk of developing serious cases of COVID-19.

Cancer researchers were uniquely positioned to respond to the challenges posed by COVID-19, and they have played a vital role in combating the pandemic while continuing their quest to cure cancer. Yet the pandemic also took its toll on cancer research, treatment, and prevention initiatives. The staggering delays in clinical trial activations and disruptions to ongoing trials resulted in significant financial losses and jeopardized trial outcomes. Also, cancer screenings have yet to return to prepandemic levels, contributing to a likely increase in more advanced cancer diagnoses in the years ahead.

The pandemic also exposed the need for greater investments in public health and medical research and led to a watershed moment for modernizing how patients receive care. Under the CARES Act, the Centers for Medicare & Medicaid Services (CMS) flexibilities to expand telehealth services are only permitted during the public health emergency. As a result, without congressional action, when the public health emergency ends, so would the CMS coverage of expanded telehealth.

The AACR Call to Action builds on what was learned during the public health emergency and lists steps that should be taken to rebuild our public health infrastructure, enhance medical research, and modernize how patients receive care and enroll in clinical trials.

INVEST IN MEDICAL RESEARCH AND THE HEALTH CARE WORKFORCE

- Offset pandemic-related research costs by providing at least $10 billion for NIH and its grantees in emergency supplemental funding as proposed in the Research Investment to Spark the Economy (RISE) Act of 2021.
- Increase investments in cancer research, treatment, and prevention by supporting robust, sustained, and predictable growth for NIH and NCI, including at least $3.5 billion and $1.1 billion, respectively, in Fiscal Year 2022 for a total funding level of $46.4 billion for NIH and $7.6 billion for NCI.
- Expand tax policies to encourage philanthropic giving so that nonprofit cancer research organizations can continue to fund high-risk, high-reward research proposals and accelerate the discovery of new cancer treatments and cures.

REBUILD THE PUBLIC HEALTH INFRASTRUCTURE AND STRENGTHEN PANDEMIC RESPONSE

- Develop a multiyear investment strategy to rebuild capacity of state, local, and federal public health infrastructures, including the health care workforce and the Strategic National Stockpile, so that the United States will be in a better position to combat future pandemics.
- Empower public health officials to speak directly to the public about the science of health emergencies and invest in a comprehensive national public health data reporting system to better track public health threats and all diseases, including cancer.
- Support CDC's National Center for Chronic Disease Prevention and Health Promotion to reduce the incidence of comorbid chronic conditions that increase the risk of developing cancer or severe symptoms from infectious diseases. These investments should include $559 million in FY 2022 for Cancer Prevention and Control Programs to support comprehensive cancer control, cancer registries, and screening, and devise targeted strategies for public awareness campaigns designed to encourage and build on prepandemic screening levels.

EXPAND ACCESS TO HEALTH CARE AND TELEHEALTH

- Enact policies that broaden health care coverage and reduce inequities in access to health care, such as expanding Medicaid.
- Deliver a permanent extension of CMS-approved telehealth services and support greater access to telehealth by providing funding, including grants, to support high-speed broadband, reach underserved areas, and address the digital divide.

STRENGTHEN AND MODERNIZE CLINICAL TRIAL DEVELOPMENT

- Support FDA's regulatory science initiatives and advance the development of oncology products by providing an increase of at least $343 million in discretionary budget authority in FY 2022.
- Increase diversity in clinical trials and alleviate the financial burden on prospective trial participants by reimbursing patients for ancillary trial-related costs, such as transportation and lodging, as contained in the DIVERSE Act.

The past two years have been some of the most challenging times ever faced by the United States and the entire world. Almost one million Americans have died from COVID-19, and millions more continue to suffer from long-term symptoms and major disruptions to everyday life. The pandemic also highlighted the crucial need for robust investments in medical research and the health care workforce. Cancer researchers and physicians have been on the front lines helping to develop safe and effective COVID-19 vaccines and treatments at a record pace as well as caring for severely ill patients with cancer.

In the face of the current health crisis due to the COVID-19 pandemic, cancer and other diseases continue to be major ongoing challenges. If we are to reach the day when cancer is no longer a major health threat to our nation's citizens, Congress must provide the significant funding that is crucial for research supported by NIH and NCI. All stakeholders must also take the necessary steps to strengthen our nation's public health infrastructure and the health care workforce so that we are better prepared for any future crises. Robust, sustained, and predictable annual funding increases for the federal agencies dedicated to advancing public health will foster future scientific advances, maximize returns from prior investments in medical research, drive economic prosperity, and support new lifesaving breakthroughs for citizens of the United States and around the world.

A SNAPSHOT OF THE IMPACT OF COVID-19 ON CANCER RESEARCH AND PATIENT CARE

STATE OF THE COVID-19 PANDEMIC

As of January 1, 2022, the U.S. share of:
Global Population: **4.25%**
Global COVID-19 Cases: **19%**
Global COVID-19 Deaths: **15%**

Individuals/Populations at an Increased Risk of Severe COVID-19

Older adults

Individuals with certain underlying conditions, such as cancer

Males

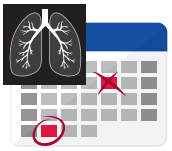
Racial and ethnic minorities and other medically underserved populations

As of January 1, 2022, FDA approvals/authorizations for COVID-19 include:

3 Vaccines 

10 Treatments 

NEGATIVE IMPACT OF COVID-19 ON CANCER RESEARCH AND PATIENT CARE



COVID-19 **significantly delayed routine cancer screening** as experienced by **Wenora Johnson** (see p. 60) and caused treatment modifications for patients with cancer, such as **Federico de Armas Heinzen** (see p. 64).

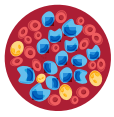
The pandemic **impaired referrals for preliminary cancer diagnoses** and led to **an increase in patients diagnosed with inoperable or metastatic cancer**. There are **serious concerns** that this trend, if continued, will **increase overall cancer morbidity and mortality in coming years**.

COVID-19 has severely disrupted the cancer research continuum including clinical trials; according to a recent AACR survey, **99% of the cancer researchers** who responded (n=66) **indicated that the pandemic interrupted their cancer research and/or clinical practice**.

COVID-19 BURDEN IN PATIENTS WITH CANCER

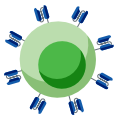
Patients with cancer, such as **Julie Campbell** (see p. 46) and **Rachel Orth** (see p. 66), **are at an increased risk for COVID-19 infection and severe disease**.

Among patients with cancer, **most vulnerable** are individuals:



With Hematologic Cancers

With Lung Cancer



Receiving B-cell targeted treatments

Most patients with cancer develop **strong immune response to COVID-19 vaccines**. However, **patients with hematologic cancers and/or those receiving B-cell depleting treatments** (e.g., CAR T-cell therapy), such as **Larry Saltzman, MD** (see p. 52), may not be optimally protected because they respond poorly to vaccines.

FUTURE OF CANCER SCIENCE AND MEDICINE BEYOND COVID-19

COVID-19 necessitated **patient-centric changes to cancer clinical trials**, allowing patients with cancer, such as **Allyson Pile** (see p. 68) to have continued access to lifesaving cancer care.

38 TIMES higher

In July 2021, the **use of telehealth** was 38 times higher than before the pandemic, with **43 percent** of users **wanted to continue using telehealth** for health care needs after COVID-19.

Decades of investments in cancer science and medicine led to the development of **mRNA-based COVID-19 vaccines** at an unprecedented speed and has renewed enthusiasm for **mRNA-based cancer vaccines**.

UNDERSTANDING THE COVID-19 PANDEMIC

In this section, you will learn:

- The global health crisis caused by the rapid spread of COVID-19 was declared a pandemic by the World Health Organization (WHO) on March 11, 2020.
- As of January 1, 2022, nearly 55 million people in the United States had been diagnosed with COVID-19, and nearly one million people had died from the disease.
- COVID-19 is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- Older adults, males, and individuals of any age with certain underlying medical conditions, including cancer, are at an increased risk for severe COVID-19 illness.
- Individuals from racial and ethnic minorities have been disproportionately impacted by COVID-19 for many of the same reasons that they shoulder a disproportionate burden of cancer.
- Viruses constantly change through alterations in their genetic material, giving rise to new variants. Many variants of SARS-CoV-2 have emerged since the onset of the outbreak.
- COVID-19 vaccines are currently widely available for all individuals age 5 years and older. The vaccines that have been approved or authorized for use in the United States are safe and effective and reduce the risk of severe illness from COVID-19.
- The FDA has approved or authorized several treatments for the management of patients with COVID-19, and there are numerous additional agents that are being evaluated in clinical studies.

The years 2020 and 2021 will be inextricably linked to COVID-19, the disease caused by the virus SARS-CoV-2, which has taken more than 5.4 million lives worldwide and caused unimaginable damage across the globe.

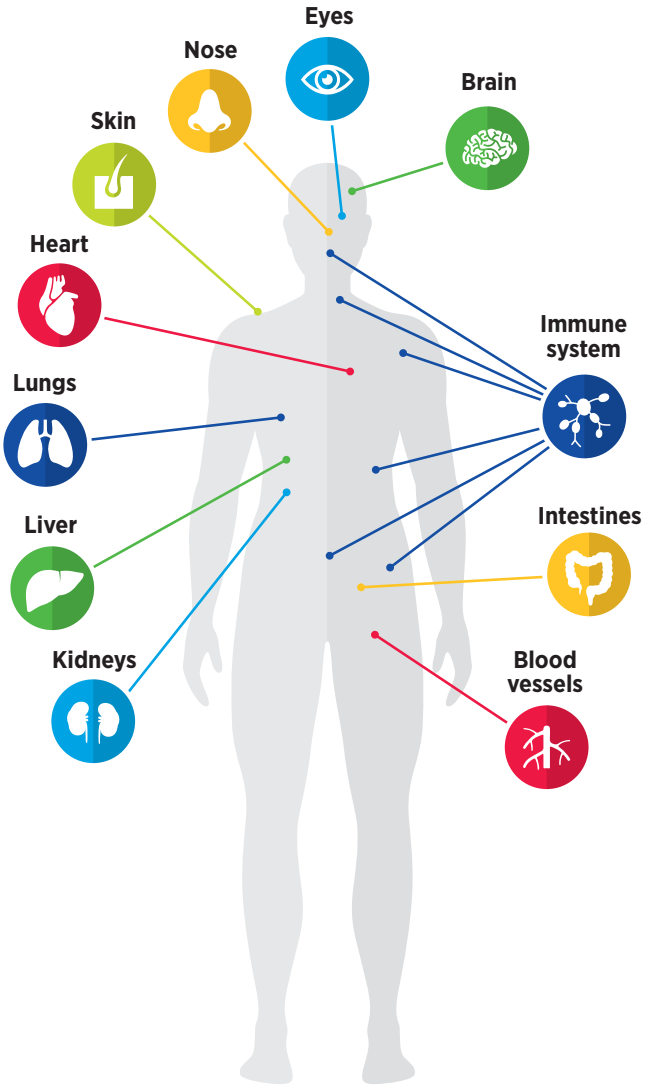
According to the World Health Organization (WHO), a disease presenting as pneumonia with unknown origins was identified at the end of 2019 in Wuhan, a city in the Hubei Province of China. In early January 2020, the Chinese Center for Disease Control and Prevention identified the underlying cause to be a novel coronavirus, the genetic sequence of which was published shortly thereafter. The International Committee on Taxonomy of Viruses termed the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and in February 2020, WHO designated the disease as Coronavirus Disease 2019, or COVID-19 (1). Within months of its onset, COVID-19 spread around the world, and on March 11, 2020, WHO declared the ensuing global health crisis a pandemic (see sidebar on **Timeline of the COVID-19 Pandemic**, p. 12). It is now established that COVID-19 predominantly spreads from person to person when an infected individual coughs, sneezes, or talks, releasing droplets that contain the virus into the air. These droplets can enter mouths or noses of people who are nearby, or can possibly be inhaled into the lungs. Although best known as a disease of the lungs, COVID-19 can affect many organs of the body in addition to the lungs (**Figure 1**, p. 11). In severe cases, COVID-19 causes pneumonia and acute respiratory distress syndrome (ARDS), which are associated with difficulty in breathing and low blood oxygen levels. If unchecked, ARDS can progress to respiratory failure, which is the cause of death in many fatal cases.

In the United States, **COVID-19** was the **third leading cause of death** in 2020, after heart disease and cancer (2).

As of January 1, 2022, more than 289 million people worldwide have been diagnosed with COVID-19 and more than 5.4 million people have died from the disease. Beyond the personal toll, the COVID-19 pandemic has overwhelmed health care systems, devastated societal norms, and disrupted the U.S. and global economies (7). The pandemic has taken an especially heavy toll on medical research and health care, including cancer research and patient care, the world over (see sidebar on **Impact of COVID-19 on Cancer Care Across the Globe**, p. 59). According to a poll conducted during the early phase of the pandemic, 48 percent of U.S. adults or their family members missed medical care due to the outbreak (8). At the onset of the pandemic, any basic and translational research not directly related to COVID-19 was halted, while cancer researchers found

FIGURE 1 THE MULTIORGAN IMPACT OF COVID-19

Coronavirus Disease 2019 (COVID-19) is best known as a disease of the lungs. In severe cases it can cause pneumonia and acute respiratory distress syndrome (ARDS), which are associated with difficulty breathing and low blood oxygen levels. If unchecked, ARDS can progress to respiratory failure, which is the cause of death in many fatal COVID-19 cases. As physicians and researchers learn more about COVID-19, an increasing number of organs and organ systems beyond the lungs appear to be affected by the disease, and many effects could be potentially long-lasting (3). Among parts of the body most frequently affected by COVID-19 are the heart, brain, kidneys, liver, intestines, blood vessels, blood, and immune system. Understanding the effects on blood vessels, blood, and immune system is a particularly active area of research investigation because an overactive inflammatory response and abnormal blood clotting are emerging as important factors in severe disease. Effects of COVID-19 on the skin, liver, eyes, and nose have also been reported in some patients. Researchers are investigating whether the multiorgan failure is a direct effect of SARS-CoV-2 infection of the organs, or if it is induced indirectly by an overactive immune response, infiltration of immune cells into the organs, dysfunction of cells that line blood vessels, or by blood clotting abnormalities. Further knowledge of the mechanisms of multiorgan damage associated with severe COVID-19 will help to improve the outcomes for patients (4-6).



ways to contribute their expertise to address the pandemic. Clinical studies that are key to bringing lifesaving anticancer therapeutics to patients were also adversely affected (see **Impact on Discovery Science and Clinical Studies**, p. 57). Although some cancer clinical trials were able to continue during the worse episodes of the pandemic and many others have resumed since then with new adaptations, the full impact of COVID-19 on cancer drug development is yet to be realized.

72 percent of U.S. adults say they **know someone who has been hospitalized or died** due to **COVID-19** (9).

The *AACR Report on the Impact of COVID-19 on Cancer Research and Patient Care* will provide a brief overview of the underlying biology of COVID-19 and cancer, present the current evidence on the burden of COVID-19 among patients with cancer, describe the disruptions caused by the pandemic on the cancer research and care continuum including the workforce, and highlight the opportunities ahead for the cancer community that were brought into focus because of the COVID-19 pandemic.

UNDERSTANDING THE BIOLOGY OF COVID-19 AND CANCER

Evidence suggests that patients with cancer are more likely to develop severe COVID-19 and die from the disease (see **Burden**

TIMELINE OF THE COVID-19 PANDEMIC

DEC 2019
- Cases of pneumonia, detected in Wuhan, China, are first reported to WHO.

JAN 2020
- China announces that the unknown pneumonia cases in Wuhan are not SARS or MERS.
- Chinese authorities identify the virus as a novel coronavirus, initially named 2019-nCoV by WHO.
- The Wuhan Municipal Health Commission announces the first death caused by the coronavirus.
- WHO confirms cases of infection outside mainland China (Japan, South Korea, and Thailand).

- SARS-CoV-2 genome is sequenced.
- The U.S. NIH announces it is working on a vaccine against the coronavirus.

- The first case of COVID-19 is confirmed in the United States.
- The White House forms a new task force to monitor and contain the spread of the virus.
- The U.S. reports first confirmed case of person-to-person transmission of the coronavirus.
- WHO declares the outbrеak a Public Health Emergency of International Concern.

FEB 2020
- The first COVID-19 death is reported outside mainland China.

- The official names COVID-19 and SARS-CoV-2 are issued by WHO.
- First COVID-19 death in the U.S. is noted; the link is not confirmed until April 2020.
- First death from the outbreak in Europe and first case in Africa are announced.
- NIH announces a clinical trial to evaluate the safety and effectiveness of the antiviral drug remdesivir in adult COVID-19 patients.
- CDC reports the first U.S. case of community spread.

MAR 2020
- CDC expands its guidance for COVID-19 testing beyond those hospitalized and those with close contact with confirmed cases and recommends that clinicians determine if a patient should be tested based on symptoms.

- WHO declares the COVID-19 outbreak to be a pandemic.
- The U.S. president declares a national emergency and releases $50 billion in federal resources to combat COVID-19.
- The first pan-cancer and cancer-specific registries (CCC19 and TERAVOLT) are launched to capture information regarding patients with cancer who also have COVID-19. Many others have since followed (see **Table 3**, p. 45).

APR 2020
- According to the Department of Labor, 6.6 million U.S. workers file for unemployment benefits in the week ending March 28, 2020, the highest number of initial claims in U.S. history.
- Globally, the total number of coronavirus cases surpasses 1 million.

- U.S. administration recommends "non-medical cloth" face coverings.
- United States passes 1 million confirmed cases of COVID-19.

MAY 2020
- FDA issues an EUA for remdesivir in hospitalized patients with severe COVID-19.
- Data collected by Johns Hopkins University report more than 100,000 COVID-19 deaths across the U.S.

JUN 2020
- Results from the UK RECOVERY clinical trial suggest that dexamethasone reduces the risk of death by a third among hospitalized COVID-19 patients requiring ventilation.
- NIH halts a clinical trial evaluating hydroxychloroquine as a treatment for COVID-19 since the drug was unlikely to be beneficial.

JUL 2020
- A vaccine being developed at the NIAID, in partnership with the biotechnology company Moderna, enters phase III testing.

AUG 2020
- FDA issues an EUA for the use of convalescent plasma (using blood of people who have recovered from COVID-19) to treat COVID-19.

OCT 2020

- FDA grants approval to remdesivir, the first approved treatment for COVID-19.

DEC 2020

- FDA grants EUA to Pfizer/BioNTech's COVID-19 vaccine, the first COVID-19 vaccine available in the U.S.
- FDA grants EUA to a second COVID-19 vaccine (Moderna).

FEB 2021
- U.S. death toll from COVID-19 exceeds 500,000.
- FDA grants EUA to Johnson & Johnson's COVID-19 vaccine, the first single dose COVID-19 vaccine available in the U.S.

MAR 2021
- WHO report suggests that SARS-CoV-2 was transmitted to people through an animal, and spread in humans no more than a month or two before it was reported in December 2019.

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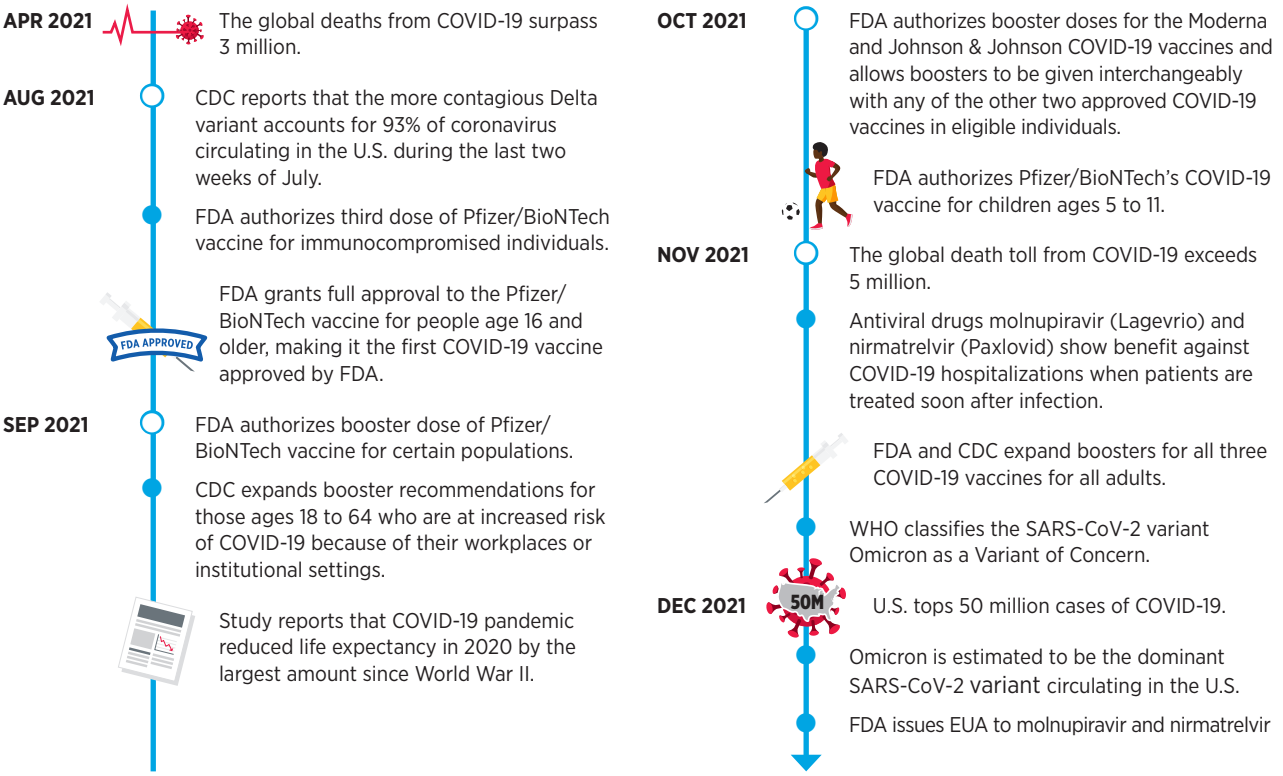
TIMELINE OF THE COVID-19 PANDEMIC (CONTINUED)



Abbreviations CDC: Centers for Disease Control and Prevention; EUA: emergency-use authorization; FDA: Food and Drug Administration; MERS: Middle East respiratory syndrome; NIAID: National Institute of Allergy and Infectious Diseases; NIH: National Institutes of Health; SARS: severe acute respiratory syndrome; U.S.: United States; WHO: World Health Organization.

of COVID-19 in Patients with Cancer, p. 41). Interestingly, certain anticancer therapeutics have shown a protective role in patients with severe COVID-19 (see **Repurposing Anticancer Agents to Treat COVID-19**, p. 40). This clinical overlap between COVID-19 and cancer calls for an examination of the biological mechanisms underpinning the development of these diseases. In the following sections we discuss the biology of the SARS-CoV-2 infection, COVID-19, and cancer development, and highlight the parallels between COVID-19 and cancer.

SARS-COV-2 INFECTION AND COVID-19

Viruses are simple microorganisms that infect cells and may cause disease. They are composed primarily of genetic material, either DNA or RNA (see sidebar on **The Basis of Genetics**, p. 14) encased in a protein "shell" called a capsid or nucleocapsid. The capsid may or may not be enclosed in a lipid membrane called the envelope; most viruses that infect animals, including SARS-CoV-2, have this envelope. Viruses can multiply only inside infected cells. To multiply, a virus must bind to and enter an appropriate host cell, where it takes over the host's cellular machinery to produce additional copies of the viral genetic materials (DNA or RNA), as well as capsid and envelope proteins, which are encoded in its genetic material. The newly formed capsids are assembled around new genetic materials and transported to the host cell surface where they consolidate with new envelope proteins and exit the host cell in a process called budding (see **Figure 2**, p. 15).

Named because of their resemblance to the solar corona, coronaviruses constitute a family of hundreds of viruses that are mostly found in birds and small mammals (e.g., bats, rodents) but have occasionally led to disease-causing infections in humans. There are seven coronaviruses, including SARS-CoV-2, that are known to infect humans; four of them cause cold-like illnesses while the other three have been responsible for the deadly global outbreaks of the respiratory illnesses severe acute respiratory syndrome (SARS) in 2002-2004, Middle East respiratory syndrome (MERS) in 2012, and COVID-19.

SARS-CoV-2 uses RNA as its genetic material and has four major structural proteins: the spike, nucleocapsid, membrane, and envelope proteins, each of which serves multiple functions (see **Figure 2**, p. 15) (12). To infect a human host, the spike protein of SARS-CoV-2 attaches to a receptor called the angiotensin-converting enzyme 2 (ACE2), which is a protein found on the surface of certain human cells in the nasal passages, lungs, and gastrointestinal tract, among others (13). Notably, prior to entering the host cell, the spike protein must be cleaved by an enzyme, called transmembrane serine protease 2 (TMPRSS2), which is also located on the surface of the host cell (13).

THE BASIS OF GENETICS

The entire set of instructions for any cell to function is encoded within its genetic material.

- The genetic material comprises deoxyribonucleic acid (DNA), a complex molecule made up of four building blocks called bases.
- The information stored in DNA is first converted into another molecule called ribonucleic acid (RNA), which is subsequently used by the cell to manufacture proteins.
- Proteins are the molecules that perform important functions that dictate a cell's fate.

Because viruses can multiply only inside infected cells, they are not considered to be alive. However, viruses have some important features in common with cell-based life. For instance, their genetic material also comprises DNA or RNA. To multiply, a virus takes over the infected cell's machinery to produce additional copies of its genetic materials.

Once SARS-CoV-2 infects human cells, it makes millions of copies of itself, which can then be breathed or coughed out to infect others. Individuals can begin shedding and transmitting virus particles within two to three days of infection, often before experiencing disease symptoms (15,16). For most individuals, it takes about three to five days after infection with SARS-CoV-2 for symptoms to appear, but for others it may take up to two weeks. Among the most reported symptoms of COVID-19 are fever and a dry cough, fatigue, muscle pain/body aches, difficulty breathing, and loss of taste and/or smell. As the disease progresses, moving from the upper to lower respiratory tract and throughout the body, there are reports of damage to nearly every organ and system in the body (see **Figure 1**, p. 11) (4,5,17). Any organ that expresses the ACE2 receptor protein, such as heart muscles, kidneys, blood vessels, liver, and the central nervous system, is vulnerable to attack. This may explain the vast array of symptoms that are experienced by COVID-19 patients. An area of ongoing research is to identify the exact mechanisms by which SARS-CoV-2 gets around inside the body; it is not yet clear whether it travels through blood or through infection of the endothelial cells that form the blood vessels. Researchers are also investigating whether the multiorgan effects of SARS-CoV-2 are induced indirectly, because of increased levels of inflammatory chemicals in the blood, endothelial cell dysfunction, blood clotting abnormalities, or infiltration of inflammatory immune cells into the organs (5). Notably, many COVID-19 patients experience long-term adverse health effects, a condition referred to as long COVID, six months or more after diagnosis, including neurocognitive, gastrointestinal, and cardiovascular symptoms, among others (18,19).

Immune Response to COVID-19

The two arms of the immune system—innate and adaptive—that make up our body's natural defense against infections as well as cancer play a critical role in defending us from viral and other pathogenic infections. Immediately after infection, mediators of the innate immune response, for example, chemicals known as interferons, are activated to limit viral multiplication and to signal the adaptive arm of immunity through mobilization of white blood cells, including B and T cells (see sidebar on **Key Cells in the Immune System**, p. 17). T cells are crucial in controlling primary infection by killing virus-infected cells. Activated B cells release antibodies that can attach to specific proteins on viruses, bacteria, and other disease-causing pathogens and prevent further infection of healthy cells. Among the different antibodies that are produced in response to a pathogen such as SARS-CoV-2, neutralizing antibodies are especially important since they bind to the virus and interfere with its ability to infect a cell. Notably, for an effective antiviral immune response, it is essential that B and T cells work in concert to destroy the virus-infected cells and neutralize the circulating viral particles.

Research has shown that once SARS-CoV-2 infects the cells of the airway in the host's lungs, it may cause massive destruction of the affected tissues. This occurs because the replication and release of SARS-CoV-2 triggers the host cells to undergo a form of cell death called pyroptosis. During pyroptosis, the damaged or dying cell releases the viral RNA and other cellular debris, which triggers neighboring cells to produce inflammatory chemicals called cytokines and chemokines that are released

The quantity of SARS-CoV-2 in a patient with COVID-19 is referred to as the viral load. **A higher viral load is associated with worse outcomes** (20).

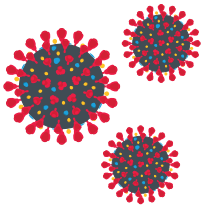
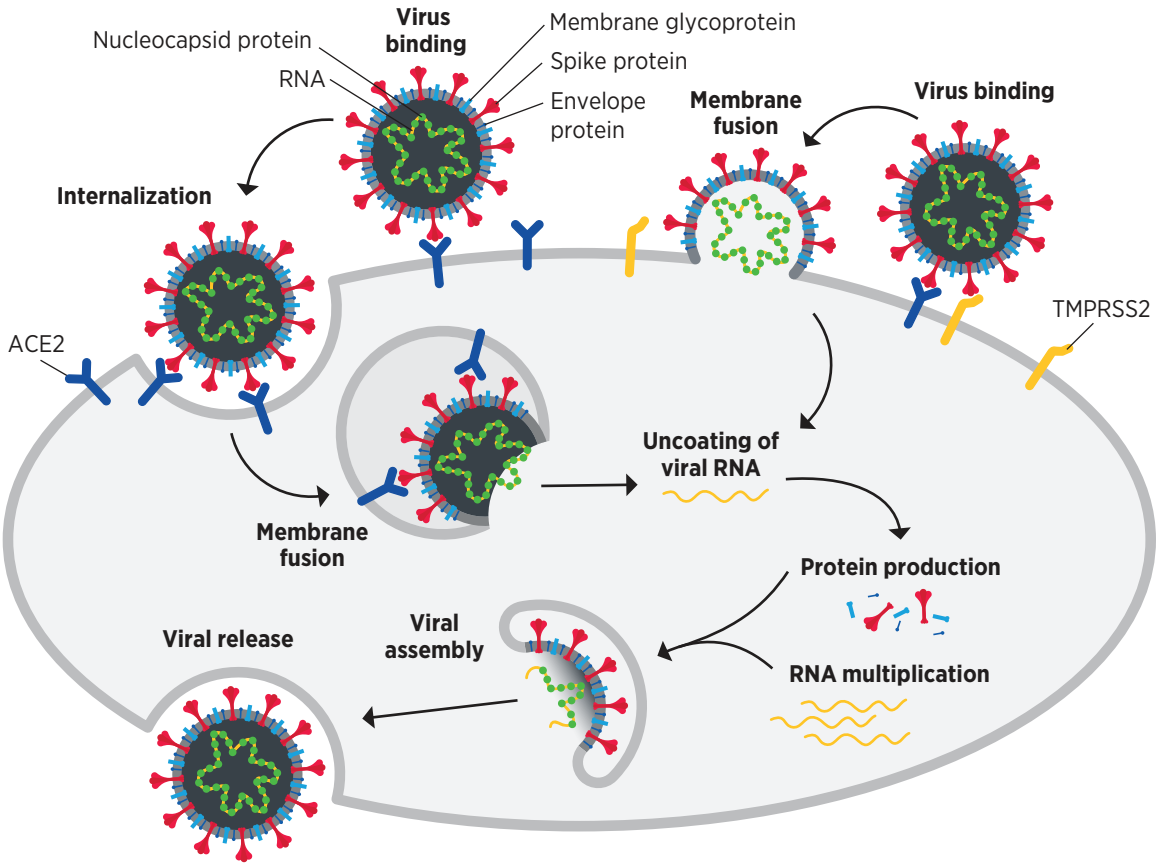


FIGURE 2 SARS-COV-2 INFECTION AND MULTIPLICATION



Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes Coronavirus Disease 2019 (COVID-19). Each SARS-CoV-2 particle contains RNA as its genetic material, encased in a "shell" formed of the nucleocapsid protein. This is enclosed in a lipid envelope. Three structural proteins pass through the lipid envelope, the envelope protein, the membrane protein, and the spike protein. SARS-CoV-2 particles can only enter cells (host) that have a protein called angiotensin-converting enzyme 2 (ACE2) on the surface. The entry is mediated by the attachment of the spike protein to ACE2 on the cells such as those lining the nasal passages and lungs. To enter cells, the virus needs another host protein, called TMPRSS2, to be present on the cell surface. TMPRSS2 modifies the spike protein, triggering fusion of the SARS-CoV-2 envelope with host cell membranes. If there are not enough TMPRSS2 protein molecules on the host cell surface, the virus can be internalized within specialized compartments in the cell where the spike is modified by a different host protein. Fusion of the viral envelope with host cell membrane allows the encased viral RNA to fully enter the host cell where it takes over the host's cellular machinery to produce copies of itself and to produce more envelope, nucleocapsid, membrane, and spike proteins. These components are then assembled into new SARS-CoV-2 viral particles which are released from the cells. The new viral particles can infect other cells or leave the body and infect other individuals.

Adapted from (6,14).

into the blood of the afflicted patients. Secretion of cytokines and chemokines attracts immune cells from the blood to the site of infection (21). In most patients, this initial immune response is enough to kill the virus and clear the infection in the lungs. However, some COVID-19 patients respond with an abnormal immune response, leading to a phenomenon known as the cytokine release syndrome (CRS) (22). CRS is characterized by high levels of inflammatory chemicals such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and others in the blood and causes severe systemic inflammation (23,24). Inflammation of the lungs can progress to acute respiratory distress syndrome (ARDS), causing difficulty breathing and low blood oxygen levels. If unchecked, ARDS can progress to respiratory failure, which is the cause of death in many fatal COVID-19 cases (22). In addition, uncontrolled CRS can lead to failure of other organs, most notably the heart, liver, and kidneys. Another

INNATE IMMUNITY	VS	ADAPTIVE IMMUNITY
First line of germ defense		Second layer of germ defense
Mediated by physical barriers (e.g., skin, mucous membranes)		Mediated by lymphatic system (lymph nodes, spleen, thymus, etc.)
Fast acting		Slow to respond
Key cellular players: neutrophils and macrophages		Key cellular players: B and T cells create antibodies for repeat offenders
Response is nontargeted and broad acting		Antibodies act against specific targets
No memory of germs killed in the past		Memory B and T cells retain memory of the germs

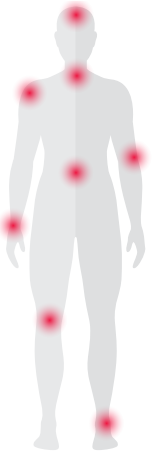
explanation for the widespread organ damage from severe COVID-19 is abnormal blood clots frequently observed in patients (25). This may arise from SARS-CoV-2 infection and damage of the endothelial cells—cells lining the blood vessels—and/or the inflammatory response due to the abnormal activation of the immune system (26). Beyond abnormal blood clotting events, COVID-19 is also associated with the formation of new and abnormal blood vessels, a phenomenon called pathological angiogenesis (27,28).

Since the onset of COVID-19, many research studies have characterized the abnormal immune activation that plays a major role in the widespread damage in patients with severe COVID-19 (29,30). These reports highlight significant dysregulation in multiple components of the immune system (30a). For instance, multiple reports have linked the severity of COVID-19 to functional errors in interferons—chemicals that, as part of the innate immune system, are released by virus-infected cells, and have the capability of limiting viral infection (30a,31). There are indications that high levels of viral multiplication during the initial phase of COVID-19 can impair an individual's ability to mount a coordinated and adequate immune response (30a). In fact, patients with severe COVID-19 display significant reduction in the numbers of many types of immune cells (e.g., CD4+ and CD8+ T lymphocytes and dendritic cells) in the blood (see sidebar on **Key Cells in the Immune System**, p. 17) (30a, 32). Additionally, researchers have noted abnormal activation of T cells as well as expression of cell-surface markers that are indicative of T cell dysfunction in patients with severe COVID-19 (30a). There are also striking anomalies in the activation pattern of B cells in patients with severe disease (29, 30a,33,34).

What is inflammation?

Inflammation refers to a **body's normal response against infections or injuries** that is **needed for the body to heal**. The process begins as certain molecules are released from the damaged tissue. In response, the immune system releases white blood cells to surround and protect the area and help repair the injury. Once the wound is healed, the inflammatory process ends.

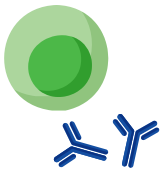
- In case of an **acute inflammation**, like a cut, the process **lasts for hours to a few days**.
- In case of **chronic inflammation**, the process may begin even in the absence of an injury and **lingers for a long time**.
  - Chronic inflammation can be associated with persistent infections, abnormal immune reactions to normal tissues, or health conditions such as diabetes, obesity, and bowel diseases, e.g., ulcerative colitis.
  - Over time, chronic inflammation may cause DNA damage and lead to cancer.



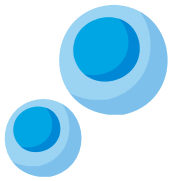
KEY CELLS IN THE IMMUNE SYSTEM

White blood cells are the cells of the immune system that work together to protect the body from pathogens such as SARS-CoV-2. They can also cooperate to attack and destroy cancer cells. Here, we briefly describe the unique functions of the white blood cells that have a central role in these processes.

B cells make antibodies (e.g., against pathogens such as SARS-CoV-2) that help the immune system function. Some remain as memory B cells to make the same antibody again later, if needed.

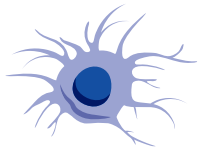


CD4+ T cells help manage the immune response. Some remain as memory T cells to fight again later.



CD8+ T cells kill infected, damaged, and cancer cells. Some remain as memory T cells to fight again later.

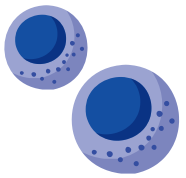
Dendritic cells educate T cells about what kinds of cells they should and should not attack.



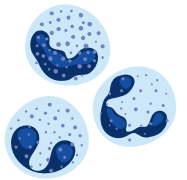
Macrophages eat foreign materials.

Mast cells release chemicals against pathogens and stimulate the immune system.

Natural killer cells kill infected, damaged, and cancer cells.



Neutrophils, **basophils**, and **eosinophils** release chemicals against pathogens and stimulate the immune system.



Adapted from (6).

While most children do not exhibit serious symptoms from COVID-19, some may develop an inflammatory syndrome following infection with SARS-CoV-2. Multisystem inflammatory syndrome of children, or MIS-C, as the condition is termed, is marked by severe inflammation of one or more parts of the body, including the heart, lungs, kidneys, brain, skin, eyes, and gastrointestinal system, and can be life-threatening (31). Ongoing research is investigating the immunological underpinnings of MIS-C as well as the potential long-term impacts on health of the infected children (35-37).

BIOLOGY OF CANCER DEVELOPMENT

Cancer is a collection of diseases that arise when the processes that control normal cell growth, division, and life span go awry. As a result, cells start to multiply uncontrollably, fail to die, acquire unique ways to obtain nutrients for survival, and begin to accumulate. In body organs and tissues, the accumulating cancer cells form masses called tumors, whereas in the blood or bone marrow they crowd out normal cells. Notably, cancer cells have unique mechanisms to escape the immune system, which normally eliminates damaged or abnormal cells. In fact, some cancer cells convince immune cells to protect the tumor instead of attacking it.

Over time, certain tumor cells may invade distant tissues, a process termed metastasis, by entering the bloodstream or the lymphatic network, and form secondary tumors at remote sites.

Alterations in the normal DNA sequence, referred to as mutations, can disrupt normal protein function, and are the leading cause of cancer development (see sidebar on **Genetic Mutations**, p. 18). Each person's cancer has a unique combination of mutations, and as cancer cells divide, new mutations arise in the daughter cells. Thus, a tumor is made up of a collection of cancer cells with a wide range of genetic abnormalities. This variation in cell types, known as heterogeneity (see **Figure 4**, p. 38), is an important part of a cancer's characteristics and fuels the cancer's ability to grow faster, escape therapy, evade the immune system, and metastasize to other organs.

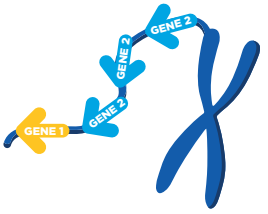
Inherited genetic mutations play a role in about 10 percent of all cancer cases; however, most mutations are acquired over an individual's lifetime due to errors arising during normal cell multiplication or because of environmental exposures, lifestyle factors, or underlying health conditions (38). While cancers are initiated due to the disruption of normal cellular functions through genetic and epigenetic changes, complex

GENETIC MUTATIONS

Mutations are changes in the genetic sequence of a cell. They may be caused by errors during cell multiplication or due to exposure to DNA-damaging agents in the environment. In the case of viruses, such as SARS-CoV-2, mutations in their genetic materials arise due to errors when the viral genome is copied during viral multiplication. Viruses also acquire mutations through a process called recombination, which occurs when two different types of viruses coinfect the same host cell and exchange their genetic material during multiplication to generate new viral variants that have some genes from both parent viruses. Mutations can be harmful, beneficial, or have no effect. Mutations in human cells may lead to cancer. Among the various types of mutations that lead to cancer are:

Extra copies of genes (gene amplification)

Higher quantities of certain proteins can result in enhanced cell survival and growth, leading to cancer.



Deletions

Loss of DNA can result in loss of genes necessary to regulate the processes that control normal cell growth, division, and life span, leading to cancer development.

Single base changes

Deletion or insertion of a single base can result in new proteins, altered versions of normal proteins, or loss of protein function, which can lead to cancer. Single base changes are also one of the most common causes of mutations in the SARS-CoV-2 genetic material.

Of note, cells acquire mutations over time, but not all mutations cause cancer. In addition, not all mutations found in a cancer cell drive cancer development.

Adapted from (38).

interactions between cancer cells and their surrounding environment—known as the tumor microenvironment—contribute to disease progression. The tumor microenvironment is a specialized niche surrounding the cancer cells and consists of immune cells—components of one's natural defense mechanism—as well as other cellular and molecular elements. Bidirectional communications between cancer cells and their microenvironment affect tumor growth and metastasis.

Intersection of COVID-19 and Cancer Biology

It is well documented that patients with cancer are more susceptible to SARS-CoV-2 infection and have a higher probability of severe disease, including mortality, from COVID-19 (see **Burden of COVID-19 in Patients with Cancer**, p. 41). This may be due to the fact that certain cancer patients have a compromised immune system attributable to their disease and/or the treatments they receive (see sidebar on **Why Are Cancer Patients at an Increased Risk of Infection?**, p. 44). The clinical association between the two diseases has led researchers to investigate the biological links between SARS-CoV-2 infection/COVID-19 and cancer, and multiple lines of evidence have emerged thus far (13,23).

Studies have shown that the expression of ACE2 protein— the receptor for SARS-CoV-2—in human lung tissue increases with age. Since cancer diagnosis is most common among those age 65 and older, it is possible that the abundance of lung ACE2 contributes to severe COVID-19 among patients with cancer (39). In addition, ACE2 levels are also shown to be elevated in the lungs of individuals who are regular smokers, including those who suffer from smoking-related lung diseases such as chronic obstructive pulmonary disease (COPD) (13,39). This may explain why smokers, or patients with smoking-related COPD or lung cancer, are especially prone to adverse outcomes from COVID-19.

Insights into a second biological link between COVID-19 and cancer have been derived from research in prostate cancer. The enzyme TMPRSS2 that cleaves SARS-CoV-2 spike protein and facilitates viral entry in human cells has been studied extensively in the context of prostate cancer. *TMPRSS2* is one of the most frequently altered genes in prostate cancer (40). TMPRSS2 protein is present in high levels in prostate cancer cells. Interestingly, the level of TMPRSS2 in the prostate is regulated by androgen, a hormone that regulates the development and maintenance of male characteristics. Ongoing research is investigating whether the level of TMPRSS2 in the lungs is also regulated by androgen, and if so, whether that explains the higher burden of COVID-19 severity in men (40). Clinical researchers are evaluating whether therapeutics that work by lowering TMPRSS2 levels or by inhibiting its function can mitigate the symptoms of COVID-19 (23,41).

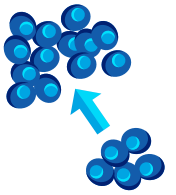
Important insights into the shared molecular mechanisms between cancer and COVID-19 have also been obtained from studies that have investigated the role of the immune system in the pathogenesis of both diseases. Both SARS-CoV-2-infected

WHAT ARE CANCER IMMUNOTHERAPIES AND HOW DO THEY WORK?

Cancer immunotherapy refers to the use of therapeutics that unleash the power of a patient's immune system to fight cancer. Not all these therapeutics, which are known as immunotherapeutics, work in the same way:

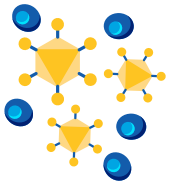
Some **release the brakes** on the natural cancer-fighting power of the immune system, for example, ipilimumab (Yervoy), nivolumab (Opdivo), and pembrolizumab (Keytruda).

Some **amplify the killing power** of the immune system by providing more cancer-targeted immune cells called T cells, for example, CAR T-cell therapies like axicabtagene ciloleucel (Yescarta).

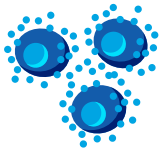


Some **enhance the cancer-killing power** of the immune system by triggering cancer-fighting T cells; these are called therapeutic cancer vaccines, for example, sipuleucel-T (Provenge).

Some **comprise a virus** that preferentially infects and kills cancer cells, releasing molecules that trigger cancer-fighting T cells; these are called oncolytic viruses, for example, talimogene laherparepvec (T-Vec; Imlygic).



Some **increase the killing power** of the immune system by enhancing T-cell function, for example, interleukin-2 (Aldesleukin).



Some **flag cancer cells** for destruction by the immune system.

Adapted from (38).

cells and cancer cells express proteins that can mark them for destruction by the immune system. Unfortunately, as research shows, both cancer cells and SARS-CoV-2 can evade the immune system by suppressing the host's defense mechanisms, e.g., by lowering levels of major histocompatibility complex (MHC)—proteins that are critical for flagging virus-infected cells or cancer cells for recognition and elimination by immune cells (23,24,42). Another mechanism of immune suppression utilized by both cancer and viral infection is "T-cell exhaustion," a phenomenon which leads to T-cell inactivation. This can occur during persistent stimulation of T cells due to chronic inflammation (often associated with cancer) or long-term infection. T-cell exhaustion is linked to adverse outcomes for patients with cancer or COVID-19. In addition, cytokine release syndrome (CRS)—the uncontrolled production of inflammatory cytokines and chemokines—a serious life-threating condition seen in patients with severe COVID-19 is also a known adverse event experienced by certain cancer patients treated with chimeric antigen receptor (CAR) T-cell therapy (see sidebar on **What Are Cancer Immunotherapies and How Do They Work?**, p. 19)(43). In fact, researchers have identified common biomarkers, e.g., IL-6, associated with both COVID-19 and CAR T-cell therapy-induced CRS (see **Figure 4**, p. 38) (23,24,42). These parallels between the mechanisms of CRS in cancer and COVID-19 have also prompted researchers to evaluate immunotherapy-inspired agents to mitigate the cytokine release in COVID-19. Anticancer agents that target IL-6 or its downstream effector Janus kinase (JAK) are being tested in numerous clinical studies for their ability to reduce the CRS and ARDS associated with COVID-19 (23,24,42).

COVID-19 is associated with the formation of new blood vessels in the patient's lungs, a phenomenon known as pathological angiogenesis that is also a hallmark of developing tumors. In fact, recent findings suggest that several proteins that are associated with tumor angiogenesis, such as VEGF, HIF, etc., may also be elevated in the plasma or lungs of patients with COVID-19 (27,28). These data have led to the ongoing evaluation of antiangiogenic cancer therapeutics in the treatment of COVID-19.

STATE OF THE COVID-19 PANDEMIC

As of January 1, 2022, 289,225,595 people worldwide have been diagnosed with COVID-19, and 5,440,035 people have died from the disease (44). The United States accounts for 19 percent of the recorded cases and more than 15 percent of recorded deaths from COVID-19 (44). Since the onset of the pandemic, the United States and countries across the globe have experienced several surges and ebbs in the outbreak of infections and deaths. The pandemic has caused unprecedented disruptions to the society, economy, and public health, worldwide. According to a recent analysis, COVID-19 deaths have led to a decline in life expectancy at birth—a widely used metric of population health and longevity—between 2019 to 2020, in 27 out of 29 countries included in the study (45); according to these data, U.S. males experienced the largest losses (2.2 years) in life expectancy at birth during 2020. As with

the burden of cancer, racial and ethnic minorities and other underserved populations have shouldered a disproportionate burden of COVID-19 (see **Disparities in the Burden of COVID-19 Among Certain U.S. Populations**, p. 20). In fact, it is estimated that the reductions of life expectancy for Black and Hispanic populations are 3 to 4 times higher than the reductions for white populations (46).

Since the onset of the SARS-CoV-2 outbreak, researchers across the globe have been tracking the progression of the pandemic in terms of disease epidemiology in populations as well as the evolution of the virus with time. Through molecular and epidemiological analysis, they have observed that, like other viruses, SARS-CoV-2 has been changing constantly through mutations in its genetic material (see sidebars on **Genetic Mutations**, p. 18). Of note, genetic mutations happen frequently during the multiplication of a virus, but only sometimes change the functional characteristics of a virus. Over time, mutations that do affect viral characteristics lead to the emergence of new forms or "variants" of the virus, often with different transmissibility. Scientists use a technology known as genomic sequencing to characterize SARS-CoV-2 genetic materials, monitor how it changes over time giving rise to new variants, understand how these changes may affect the properties of the virus, and use this information to predict how these new variants might impact public health.

Variants with distinct genetic alterations have emerged across the globe throughout the pandemic that were first noticed in the U.K. (Alpha variant), South Africa (Beta and Omicron variants), Brazil (Gamma variant), and India (Delta variant) (see sidebar on **SARS-CoV-2 Variants**, p. 21). While these variants shared some of the same genetic mutations, they all emerged independently. The Delta variant, which was first detected in India ignited new surges of COVID-19 infections across the globe including in the United States (47). The Delta variant was found to be far more transmissible than prior variants of SARS-CoV-2 and was the most dominant strain in the United States until mid-December 2021 (48,49). Despite the higher transmissibility, available data are somewhat encouraging and show that the rates of hospitalization and severe disease were not different during the time period when the Delta variant was the predominant strain in the U.S. compared to the earlier periods in the pandemic (50).

In November 2021, a new variant associated with a concerning rise of COVID-19 cases was first detected in Botswana followed by South Africa and reported to the WHO by public health officials in South Africa (51-53). The variant, named Omicron, has since been detected in numerous additional countries and, as of January 1, 2022, is the predominant strain in the United States (54). Omicron has a variety of mutations, including over 30 in the SARS-CoV-2 spike protein alone, and has raised concerns among scientists since some of these mutations are known to be associated with reduced response to available therapeutics (55). While early studies indicate that fewer proportions of Omicron-infected patients may experience severe symptoms, the high rate of transmissibility of Omicron has led to surges in new infections, which continue to strain the health care system. Researchers are currently gathering evidence to answer definitively whether the combination of mutations allows Omicron to evade immune protection, including the protection generated by prior infection or vaccines, and whether available therapeutics are effective for patients with COVID-19 who are infected with Omicron (51,56-62).

Public health experts at CDC and worldwide are studying each SARS-CoV-2 variant to understand their differences, to monitor or predict whether a variant is more dangerous than others, and to track the spread of a variant. Experts at CDC classify certain variants as Variants Being Monitored (VBM), Variants of Concern (VOC), Variants of Interest (VOI), or Variants of High Consequence (VOHC), based on how easily they spread, how severe their symptoms are, and how they can be treated (63) (see sidebar on **SARS-CoV-2 Variants**, p. 21).

DISPARITIES IN THE BURDEN OF COVID-19 AMONG CERTAIN U.S. POPULATIONS

In the United States, which accounts for one out of five of all recorded cases of COVID-19 globally (44), a disproportionate burden of the disease has fallen on racial and ethnic minorities and other medically underserved populations (see **Inequities in the Burden of COVID-19 in the United States**, p. 23, and sidebar on **U.S. Racial and Ethnic Population Groups**, p. 22) (65).

Researchers are actively investigating the factors that have contributed to the disproportionate burden of COVID-19 among racial and ethnic minorities and other underserved populations. Most evidence suggests that there are several complex and interrelated causes, many of which overlap with the factors that contribute to cancer health disparities (65) (see sidebar on **Determinants of COVID-19 and Cancer Health Disparities**, p. 24).

Social determinants of health, defined by NCI as the conditions in which people are born, grow, live, work, and age, play a significant role in driving cancer health disparities and have emerged as some of the most important factors contributing to the stark inequities in the burden of COVID-19 (65,72-74). For U.S. racial and ethnic minorities, decades of structural and systemic racism have contributed to adverse differences in many, if not all, of these determinants. During the past two years of the pandemic, these inequities have drawn the renewed attention of public health and policy experts. For instance, it was clear that individuals who belong to racial and ethnic minorities were more likely to live in conditions that posed challenges for social distancing, which was one of the main preventive strategies for reducing infection with SARS-CoV-2 at the initial phase of the pandemic. Because of socioeconomic inequities, they are more likely to live in lower-income apartment complexes, with higher numbers of occupants per unit, and more likely to live in multigenerational family units. The same population groups are also more likely to work in occupations considered essential for society to function—such as staffing grocery stores, hospitals, nursing homes, building maintenance, forms of transportation, and delivery services—which increases their chances of being exposed to SARS-CoV-2 because they are unable to shelter at home (65).

Another important factor contributing to COVID-19 disparities is that many people from racial and ethnic minority groups are more likely to have one or more of the health conditions associated with an increase in a person's chance of severe COVID-19 compared to individuals who are white (see **Increasing Risk for COVID-19**, p. 22). Inequity

SARS-COV-2 VARIANTS

The SARS-CoV-2 Interagency Group (SIG) established by the U.S. Department of Health and Human Services coordinates efforts across CDC, NIH, FDA, Biomedical Advanced Research and Development Authority, and the U.S. Department of Defense to rapidly characterize emerging SARS-CoV-2 variants and monitor their potential impact on critical COVID-19 mitigation measures, including vaccines, therapeutics, and diagnostics (63). WHO also classifies variants (64). To ease public discussions of variants, WHO proposed labeling variants based upon the Greek alphabet. U.S. classifications may differ from those of WHO because the impact of variants may differ by location.

SIG meets regularly to evaluate the risks posed by SARS-CoV-2 variants circulating in the United States and to make recommendations about the classification of variants under four categories in order of increasing clinical significance*. The following list includes variants that have been characterized as of January 1, 2022:

Variants Being Monitored

Variants for which there are data indicating a potential or clear impact on clinical interventions or that have been associated with more severe disease or increased transmission but are no longer detected or are circulating at very low levels in the United States, and do not pose a significant and imminent risk to U.S. public health. A **Variant of Interest** or a **Variant of Concern** may be downgraded to this category when there is a significant and sustained reduction in its prevalence, or if evidence indicates that a variant does not pose significant risk to U.S. public health.

- Alpha, Beta, Gamma, Epsilon, Eta, Iota, Kappa, Mu, Zeta

Variants of Interest

Variants with characteristics that have been associated with changes to receptor binding, reduced immunity from previous infection or vaccination, decreased efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or disease severity.

- As of January 1, 2022, there are no SARS-CoV-2 Variants of Interest in the U.S.

Variants of Concern

Variants for which there is evidence of an increase in transmissibility, more severe disease, significant reduction in immunity from previous infection or vaccination, reduced effectiveness of treatments or vaccines, or diagnostic detection failures.

- Delta and Omicron

Variants of High Consequence

Variants having clear evidence that prevention measures or medical countermeasures have significantly reduced effectiveness relative to previously circulating variants.

- As of January 1, 2022, there are no SARS-CoV-2 variants in the U.S. that rise to the level of high consequence.

*Given the continuous evolution of SARS-CoV-2 and our understanding of the impact of emerging variants on public health, variants may be reclassified based on their prevalence and health impact.

in access to quality health care is a key factor contributing to the higher levels of underlying health conditions that increase the risk of severe COVID-19 among people in racial and ethnic minority groups and have contributed to the higher COVID-19 burden among these populations (75). Notably, according to a recent study, Black and Hispanic individuals irrespective of socioeconomic status experienced higher all-cause mortality increases due to the COVID-19

U.S. RACIAL AND ETHNIC POPULATION GROUPS

When federal agencies collect data that include race and ethnicity, the agencies follow the Office of Management and Budget (OMB) Statistical Policy Directive No. 15, Race and Ethnic Standards for Federal Statistics and Administrative Reporting (66). The racial and ethnic OMB categories are:

African American or Black

A person having origins in any of the Black racial groups of Africa.

American Indian or Alaska Native

A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment.

Asian

A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

Hispanic or Latino/a

A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.

Native Hawaiian or Other Pacific Islander

A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White

A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

It is important to note that data collected on race and ethnicity rely on individuals self-reporting this information. Therefore, the data may be influenced by sociopolitical constructs and may not fully reflect the individual's genetic ancestry.

pandemic compared to those who are white (74). Researchers are actively investigating whether there are biological factors contributing to racial and ethnic COVID-19 disparities (76,77). There is also deep concern that undocumented immigrants have experienced adverse differences in COVID-19 measures, in large part because of the lack of access to quality health care (78,79).

Measuring the true impact of COVID-19 on racial and ethnic minorities and other medically underserved populations will require collection and reporting of high-quality, accurate information on race, ethnicity, and the relevant social determinants of health. Unfortunately, early in the pandemic, many state health departments experienced challenges in collecting complete or accurately classified race and ethnicity data (80). Granularity in demographic data on COVID-19 testing, cases, vaccination, hospitalizations, and deaths at a county and zip code level will allow better assessment of the impact of COVID-19, enable effective health care interventions in underserved communities, and drive public health policy. In this regard, the NIH has initiated the Rapid Acceleration of Diagnostics-Underserved Populations (RADx-UP) program to understand the factors associated with disparities in COVID-19 morbidity and mortality and to lay the foundation to reduce disparities for those underserved populations who are disproportionately affected by the COVID-19 pandemic (81).

INCREASING RISK FOR COVID-19

The presentation of disease experienced by individuals who are infected with SARS-CoV-2 covers a wide spectrum, from no symptoms to mild disease to severe disease to critical disease and even death. Advanced age (65 and older), sex (male), and having certain chronic health conditions, such as cancer; chronic kidney disease; chronic liver disease; chronic lung diseases, e.g., chronic obstructive pulmonary disease (COPD); dementia or other neurological conditions; diabetes; Down syndrome; heart conditions; HIV infection; immunocompromised state; mental health conditions; sickle cell disease or thalassemia; stroke or cerebrovascular disease; substance use disorders; and tuberculosis increase a person's risk of severe COVID-19 (82). Solid organ transplant or blood stem cell transplant and pregnancy have also been linked to an increased risk of severe COVID-19 (82).

According to a study published early in the pandemic, patients with COVID-19 who had underlying chronic health conditions are six times more likely to be hospitalized and 12 times more likely to die compared to those who had no underlying chronic health conditions (83). However, current data on hospitalization and disease severity from CDC suggest that healthy patients of any age and sex can develop severe disease (49). It should be noted that many of the conditions that increase an individual's risk for severe COVID-19 are also causally linked with cancer. For example, the U.S. population group that accounts for 55 percent of new cancer diagnoses—individuals age 65 and older— is also at high risk for severe COVID-19 and has the highest death rate compared to its proportion in the general population (49,84).

Beyond underlying health conditions, modifiable risk factors such as obesity and smoking, which are also linked to diagnoses

INEQUITIES IN THE BURDEN OF COVID-19 IN THE UNITED STATES

Not all segments of the U.S. population have shouldered the burden of Coronavirus Disease 2019 (COVID-19) equally. Examples of such disparities include:

1.5 TIMES higher	The **age-adjusted risk of COVID-19 diagnosis** is more than 1.5 times higher **among Hispanic and American Indian/Alaska Native** individuals compared to those who are white (67).
TWICE as likely	Individuals who are **American Indian/Alaska Native, Black, or Hispanic** are twice as likely to **die from COVID-19** compared to those who are white (67).
2.5 TIMES/ >3 TIMES higher	Between March 1, 2020 and December 25, 2021 the **age-adjusted rate of COVID-19-associated hospitalization** was 2.5 times higher for **Black** and more than 3 times higher for **American Indian/ Alaska Native** individuals compared to those who are white (68).
2- to 3-FOLD higher	**Age-adjusted excess death rates** (compared to what would be expected based on 2019 data) between March and December 2020 **from both COVID-19 and non-COVID-19 causes**, were two to three-fold higher for **American Indian/Alaska Native, Black, and Hispanic** individuals compared to those who are white (69).
54.1%	**People age 75 and older** account for 5.4 percent of COVID-19 cases, but 54.1 percent of deaths from the disease (49).
>2.5 TIMES higher	Among **children and adolescents ages 0-17 years, COVID-19-related hospitalizations** were more than 2.5 times higher among those who are **American Indian/Alaska Native, Black, or Hispanic** compared to those who are white (70).

of cancer, have been shown to increase the risk for severe COVID-19 (82). Therefore, it is concerning that during the COVID-19 pandemic (between 2019 and 2020), prevalence of obesity increased among youth and adults (85,86) and, according to the most recent Federal Trade Commission Cigarette Report, so did the annual cigarette sales for the first time in 20 years (87). These worrying trends underscore the urgent need for new strategies to enhance the dissemination and implementation of our current knowledge of healthy living, disease prevention, and modifiable behavioral risk factors.

Researchers are also investigating the role of genetic factors that are associated with a person's chances of becoming severely ill with COVID-19 (91). Concerted efforts from academic laboratories and the private sector have provided valuable insights into the genetic underpinnings of infection and severe disease (92-95). These studies have uncovered several genetic alterations associated with severe COVID-19. Among the genes identified are those that boost our defense against viral infections, such as members of the interferon pathway, as well as novel genes of currently unknown significance (96-98). As researchers dive deeper into the genetic, environmental, social, and other determinants of susceptibility to infection and severe illness from COVID-19, they may uncover additional factors that confer risk. These studies will also provide definitive answers to some of the pandemic's most elusive questions, such as factors that may be protective against SARS-CoV-2 infection and COVID-19. In this regard, early in the pandemic, some

DETERMINANTS OF COVID-19 AND CANCER HEALTH DISPARITIES

Complex and interrelated factors contribute to U.S. health care disparities such as the disproportionate burden of COVID-19 or cancer. For racial and ethnic minorities, adverse differences in many, if not all, of these factors are directly influenced by structural and systemic racism. The factors may include, but are not limited to, differences or inequalities in:

Socioeconomic factors

- Education
- Income
- Employment
- Health literacy and numeracy*
- English language proficiency

Clinical factors

- Access to quality health care that is culturally appropriate
- Access to health insurance
- Cultural fluency of health care providers

Environmental factors

- Transportation
- Housing
- Geographic location

Cultural factors

- Cultural beliefs
- Cultural health beliefs

Behavioral and psychological factors

- Tobacco use
- Alcohol use
- Access to healthy nutritional choices
- Access to safe spaces for physical activity
- Access and adherence to risk reduction/ preventive care
- Stress
- Access to culturally tailored mental health care

Genetic and biological factors

General health

- Having other health conditions or comorbidities

*Health literacy is understanding and evaluating basic health information to make appropriate health decisions while health numeracy is the ability to access, use, interpret, and communicate mathematical information as related to health including understanding and applying numbers required for daily self-care.

Developed from (65,71).

reports suggested that individuals with certain blood types were less susceptible to COVID-19 compared to those with other blood types (98-100). However, more recent research, including a review of more than 100,000 patients across three U.S. state health networks, found no link between blood type and COVID-19 susceptibility or severity (101-103).

Studies have unequivocally shown that patients with cancer such as **Julie Campbell** (see p. 46) are at an increased risk for COVID-19 (see **Burden of COVID-19 in Patients with Cancer**, p. 41). Patients who have blood cancer are at the greatest risk (see **Patients with Hematologic Cancers**, p. 42). Research is underway to understand whether the higher risk of COVID-19 infection and death among patients with cancer is a result of the cancer itself, the cancer treatments, or other factors such as smoking or additional coexisting chronic illnesses. One possibility that scientists have considered is that certain patients with cancer have a compromised immune system due to their disease or the treatments, making them more vulnerable to infection (see sidebar on **Why Are Cancer Patients at an Increased Risk of Infection?**, p. 44). Notably, researchers have shown that SARS-CoV-2 infection can be persistent in immunocompromised individuals such as certain patients with cancer, with reports of individuals who shed the virus for 70 days or those who stayed infected for nearly one year (104,105). These findings raise the concern that the virus may develop mutations and give rise to new variants in immunocompromised individuals who suffer from long-term SARS-CoV-2 infection (106). Public health experts are especially worried about the possibility that persistent SARS-CoV-2 infection may generate more transmissible or more pathogenic SARS-CoV-2 variants (107). Therefore, concerted efforts must be made to prevent immunocompromised patients with cancer from contracting COVID-19 through prioritized vaccination (if/when public health experts consider additional primary or booster doses) or other preventive measures, not only to protect them from the risk of severe disease and its long-term sequelae, but also to reduce the likelihood of new viral variants. It is equally important to ensure that patients

There is clear evidence that **obesity is a risk factor for severe COVID-19 outcomes**, even among younger patients (88,89).

Obesity is **associated with chronic inflammation** and is a risk factor for many additional diseases, including cancer (38).

Therefore, it is **concerning that children, adolescents, and young adults ages 2 to 19**, who were already overweight or obese before the pandemic, **experienced significant weight gain during the pandemic** (90).

with cancer are adequately represented in clinical trials assessing the safety and effectiveness of vaccines and treatment for COVID-19. Without such research, we cannot ensure that preventive and therapeutic agents will benefit this particularly vulnerable population.

DETECTION, PREVENTION, AND CLINICAL MANAGEMENT OF COVID-19

Timely testing to identify those who are or have been infected with SARS-CoV-2 is a crucial step in understanding and reducing the spread of COVID-19. Some viral tests look for current infection (see sidebar on **How Can We Test for SARS-CoV-2?**, p. 26). The knowledge gathered from these tests is critical for the implementation of appropriate measures to prevent further spread of the virus and to understand when such measures can be eased. Additionally, certain tests can identify whether an individual had a past infection, although the utility of these tests has been highly debated (108). SARS-CoV-2 tests can be performed at a health care facility, a designated testing site, or at home using a self-test kit.

Since the onset of the COVID-19 outbreak, the U.S. Food and Drug Administration (FDA) has worked with test developers from the private and academic sectors to streamline the testing process and make more tests available to all citizens. To address the urgency of SARS-CoV-2 detection in limiting spread and controlling the pandemic, FDA has allowed for three independent pathways for the development of coronavirus tests (see sidebar on **How Can We Test for SARS-CoV-2?**, p. 26) (109). It is important to note that no test is 100 percent accurate all the time, and there are some individuals who may receive a false-positive or a false-negative result. Individuals who think that they may have COVID-19 should immediately talk to their health care providers about getting tested. It is also important to discuss the type of test they received and the outcomes to understand what their results mean and to determine the next steps. CDC provides detailed guidelines on who should be tested, which test should be used, how to get a SARS-CoV-2 test, and what to do in case a positive test result is received (110).

In addition to diagnostic testing, CDC has recommended the identification of symptomatic and asymptomatic infected individuals through the process of contact tracing, to control the spread of COVID-19 (112). Contact tracing is key to slowing the spread of infectious diseases such as COVID-19 when implemented with necessary additional measures such as isolation or quarantine (113), and treatment, and helps protect infected individuals, their families, and their communities (114). In the United States, individual state and local Departments of Health have been primarily responsible for contact tracing, with some state-level collaborations with community partners (115,116). Digital technologies in the form of symptom and contact tracing apps for smartphones have also been used to track new COVID-19 cases and identify "hot spots" of infection in real time (117-120). This information can potentially allow local hospitals and health care systems to better prepare for surges in new cases. Large sets of data collected through contact tracing apps can also be used by researchers to deepen scientific understanding of SARS-CoV-2 and the symptoms related to COVID-19, as well as to identify potential risk factors and disparities related to infection and disease severity (121,122). However, ongoing research is needed to determine ways to overcome the technical and ethical challenges that have emerged as the primary obstacles toward the widespread implementation of these tools.

Because cancer patients are more vulnerable to infection (see sidebar on **Why Are Cancer Patients at an Increased Risk of Infection?**, p. 44), and could be at a high risk for severe COVID-19 (see **Burden of COVID-19 in Patients with Cancer**, p. 41), preventing infections in this vulnerable population has been a priority for health care providers since the onset of the pandemic. Depending on the location (e.g., areas with high rates of ongoing community transmission), the availability of COVID-19 diagnostic tests, and/or the type of cancer, many health care institutions implemented either universal testing of patients with cancer or testing of asymptomatic patients who were scheduled to receive certain anticancer therapeutics (123-127). Health care professionals strongly recommend that patients with cancer speak with their health care provider teams to decide when and if a COVID-19 detection test is needed for them.

PREVENTION OF COVID-19: VACCINES

As our knowledge of the spread of SARS-CoV-2 accumulated, CDC recommended several prevention strategies: washing hands frequently; avoiding close contact with people who don't live in the same household by staying six feet apart; covering mouth and nose with a well-fitting mask when around other people; covering mouth and nose when coughing and sneezing; cleaning and disinfecting frequently touched surfaces daily; and monitoring health daily. Prior to the authorization of the SARS-CoV-2 vaccines, these prevention strategies were the only ways to limit infection with the virus and, therefore,

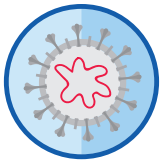
HOW CAN WE TEST FOR SARS-COV-2?

There are two types of SARS-CoV-2 tests: **diagnostic tests** and **antibody tests**.

Diagnostic Tests

- Determine if a patient is currently infected with SARS-CoV-2; cannot determine if a person was previously infected.
- The samples tested are nasopharyngeal, nasal, or throat swabs, or saliva samples.
- Currently there are two types of diagnostic tests.

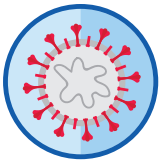
Molecular tests



The sample is tested using a technique called polymerase chain reaction (PCR) that detects the virus's genetic material.

- Take more time than antigen tests, i.e., results can take up to three days.
- More sensitive compared to an antigen test
- Less chance of inaccurate results compared to an antigen test

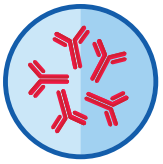
Antigen tests



The sample is tested using techniques that detect specific proteins, called antigens, on the surface of the virus.

- Quicker than molecular tests, i.e., results can be available within few hours.
- Less sensitive compared to a molecular test
- More chance of inaccurate results compared to a molecular test, e.g., may miss some people who are infected

Antibody Tests



- Determine if a patient was previously infected with SARS-CoV-2; cannot determine if a person is actively infected.
- The samples tested are blood samples.
- The sample is tested to determine whether proteins called antibodies that the patient's immune system would have made during a previous infection with SARS-CoV-2 are present.

To address the urgency of controlling the COVID-19 pandemic FDA has allowed for three independent pathways for the development of SARS-CoV-2 tests (106):

Emergency Use Authorization (EUA) – EUA provides faster access to critical medical products that may help during an emergency when there are no adequate, approved, and available options. To issue an EUA, FDA quickly evaluates the evidence that is currently available, carefully balancing the risks and benefits of a product as known at the time, among other criteria.

Lab Developed Test (LDT) – LDT is a diagnostic test that is manufactured by and used within a single laboratory. The Centers for Medicare & Medicaid Services regulates most laboratory testing performed on humans in the U.S. through the Clinical Laboratory Improvement Amendments (CLIA). During the pandemic, FDA has provided flexibility to certain laboratories certified under CLIA to run COVID-19 tests. Laboratories that develop and perform their own testing must validate the test, notify FDA, and submit the validation data to FDA within a certain time as part of an EUA request.

State Authorization – FDA has provided flexibility to states that want to authorize laboratories certified to conduct high-complexity tests in that state to develop and perform COVID-19 testing. Under this policy, the state takes responsibility for the safety and accuracy of the tests and the laboratory does not submit an EUA request to FDA.

As of **January 1, 2022** there were **419 tests** and sample collection devices authorized by FDA under EUAs. These include **290 molecular** tests and sample collection devices, **87 antibody** and other immune response tests, and **42 antigen** tests. Detailed information on all of these tests is provided by FDA (111).

Mask wearing can reduce new COVID-19 cases by 53 percent (129).

For complete CDC guidelines on how individuals can protect themselves against COVID-19, see https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html

minimize the morbidity and mortality of COVID-19. It should be noted that these strategies are still recommended for individuals who are not fully vaccinated or those who have a weak immune system (128).

Vaccines are compounds that trigger the immune system to respond to a pathogen, such as a bacterium or virus, or to a tumor. A vaccine can help the body recognize and destroy cancer cells or microorganisms. When viruses such as SARS-CoV-2 infect our bodies, the immune system responds with cellular and molecular tools to fight off the infectious pathogen (see sidebar on **Key Cells in the Immune System**, p. 17). Once a person is infected, it takes several days or weeks for the immune system to generate all the cellular and molecular tools needed to eradicate the infection. Even after the infection is cleared, the individual's immune system remembers what it learned about protecting the body against that pathogen (130). COVID-19 vaccines are the only known safe and effective way to help our bodies develop immunity to SARS-CoV-2 without having to get the illness.

Vaccines that prevent SARS-CoV-2 infection are considered the most promising approach to control the COVID-19 pandemic. Soon after the onset of the COVID-19 outbreak all stakeholders in the global research community came together in an unprecedented manner and worked collaboratively to generate safe and effective vaccines against COVID-19. In the United States, significant investments and accelerated regulatory policies provided by federal agencies including NIH, FDA, and CDC, as well as public–private partnerships such as Operation Warp Speed, brought tremendous resources to tackle this challenge, as discussed by **Senator Roy Blunt** (see p. 78). As a result, in less than a year after the identification of SARS-CoV-2 as the causative agent of COVID-19, researchers delivered multiple vaccines capable of eliciting immunologic protection and helping limit the spread of COVID-19 (see sidebar on **SARS-CoV-2 Vaccination Recommendations**, p. 27) (131).

Currently, there are three COVID-19 vaccines (produced by three different biopharmaceutical companies) that are authorized for use in the United States: BNT162b2 or Comirnaty (Pfizer-BioNTech), mRNA-1273 (Moderna), and JNJ-78436735 (Janssen). While these vaccines work in different ways, they are all safe and effective against COVID-19 infection and severe disease (134). CDC has a preference for the two mRNA vaccines, BNT162b2 and mRNA-1273. BNT162b2 and mRNA-1273 contain fragments of a type of nucleic acid called mRNA which when injected into the body instructs certain immune cells to produce a harmless version of the SARS-CoV-2 spike protein and display fragments of the protein on the cell surface (**Figure 3**, p. 29). These fragments are recognized by the body's immune system leading to the production of antibodies and the activation of a wide array of protective immune cells (130,135). The process trains the immune system on how to defend against a potential future attack from the actual virus. JNJ-78436735, a viral vector vaccine, is an inactivated version of SARS-CoV-2 which, when injected, instructs the body's cells to produce a harmless version of the spike protein leading to activation of the immune system and protection against future infection from the actual virus.

Bringing a new vaccine from the bench to the clinic involves many steps, including laboratory research, clinical trials, FDA review and approval, large-scale manufacturing, and distribution. While COVID-19 vaccines were developed rapidly, all stakeholders in the medical research community worked diligently to take the necessary steps to ensure their safety and effectiveness. It is also important to note that the foundation of the research leading to SARS-CoV-2 vaccines was laid decades ago with fundamental basic science in understanding the biology of prior coronaviruses such as SARS and MERS, mechanisms of vaccine-induced immunity, protection from viral infections, strategies to use mRNA to induce an immune response, and pathways by which the immune system generates antibody responses to parts of coronaviruses (131). The vaccine delivery platforms that form the backbone of the SARS-CoV-2 vaccines had also been under development and were already tested in

DID YOU KNOW?

- COVID-19 vaccines **cannot cause** infection with SARS-CoV-2 or other viruses.
- COVID-19 vaccines **do not affect or interact with** our DNA in any way.
- The mRNA or the **spike protein generated** from the COVID-19 vaccines **does not last long in our bodies**.
- **Many people have no reaction to vaccination**, while **some have common side effects** such as pain or swelling at the injection site, headache, chills, or fever. These reactions are **normal signs that the body is building protection**. Reports of serious adverse events after vaccination are rare and are closely monitored by CDC and FDA (136).

SARS-COV-2 VACCINATION RECOMMENDATIONS

As of January 2022, there were three COVID-19 vaccines authorized or approved for use in the United States. The vaccines are safe, effective, and reduce risk of severe illness from COVID-19. It must be noted that the guidance for vaccination continues to evolve rapidly. Individuals must consult with their health care providers to learn the most up to date recommendations.

Between December 2020 and November 2021, an estimated 1.1 million additional COVID-19-attributable deaths were averted in the United States because of vaccination (132).

It is important to note that, while the vaccines are highly effective in preventing infection and severe disease, vaccinations cannot mitigate COVID-19 once an individual is ill with the disease.

BNT162b2 or Comirnaty (Pfizer-BioNTech)*

Age – CDC recommends vaccination for individuals age 5 and older.

Regimen – Primary series: Two doses are recommended, administered three weeks apart; individuals who are moderately or severely immunocompromised (such as patients on active cancer treatment) should get an additional dose 28 days after the second shot.

Booster dose†,‡ – Recommended for all adults age 12 years and older at least five months after their second dose.

mRNA-1273 (Moderna)*

Age – CDC recommends vaccination for individuals age 18 and older.

Regimen – Primary series: Two doses are recommended, administered four weeks apart; individuals who are moderately or severely immunocompromised (such as patients on active cancer treatment) should get an additional dose 28 days after the second shot.

Booster dose† – Recommended for all adults age 18 years and older at least five months after their second dose.

JNJ-78436735 (Janssen)*

Age – CDC recommends vaccination for individuals age 18 and older.

Regimen – Primary series: One dose.

Booster dose† – Recommended for all adults age 18 years and older at least 2 months after first dose.

*CDC has a clinical preference for the mRNA-based vaccines BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna), over the viral-vector-based vaccine JNJ-78436735 (Janssen). A person is considered fully vaccinated against SARS-CoV-2 infection ≥2 weeks after receipt of the second dose in a 2-dose series (Pfizer-BioNTech or Moderna) or ≥2 weeks after receipt of a single dose of the Janssen COVID-19 vaccine. CDC has detailed information on the possible side effects, vaccine ingredients, and safety profiles for all vaccines (133). Individuals with a known history of allergic reactions to a COVID-19 vaccine ingredient should not get that vaccine. They may still be able to get one of the other two vaccines. If unsure, individuals should discuss with their health care providers regarding their specific health situations to decide which vaccine is right for them.

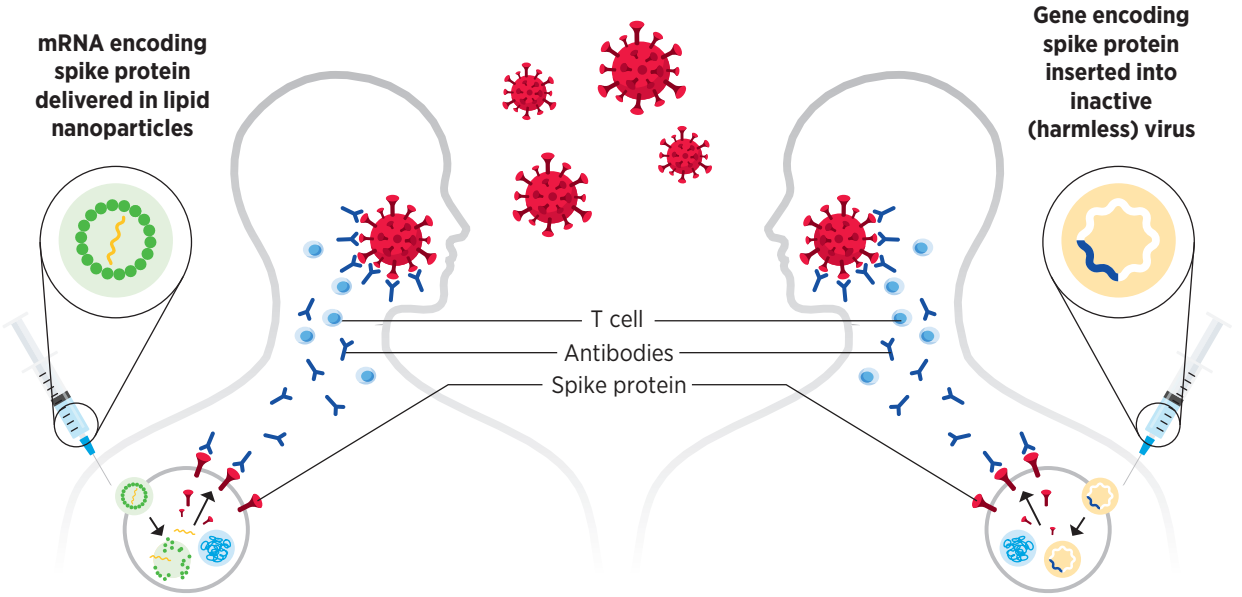
†According to CDC's recommendations, everyone age 18 and older should get a booster dose of either Pfizer-BioNTech or Moderna vaccine.

‡Teens 12-17 years old should get a Pfizer-BioNTech vaccine booster.

humans prior to COVID-19. In fact, the mRNA vaccine platform was developed and tested in humans initially as an experimental cancer vaccine (131). The rapid development of COVID-19 vaccines can therefore be attributed to decades of robust investments across all areas of medical research and unprecedented collaborative efforts from the biomedical community including key contributions from cancer researchers (see **Cancer Researchers Working to Combat the COVID-19 Pandemic**, p. 35).

Data from the vaccine clinical trials as well as use in public settings after FDA authorization (real-world data) suggest that all three vaccines currently used in the U.S. are effective, especially against severe illness, hospitalization, and death from COVID-19 (137). According to data from CDC, as of January 1, 2022, unvaccinated individuals had a five-fold higher risk of testing positive for COVID-19 and a fourteen-fold greater risk of dying from COVID-19 compared to those who are fully vaccinated (138). The level of protection is even higher for fully vaccinated individuals who have received an additional (booster) dose (138). Fully vaccinated individuals who contract COVID-19 may also be less likely to have long COVID compared to the unvaccinated although more confirmatory data are needed (130,139-141). There is also evidence that the vaccines were protective against the Delta variant which was the most common variant in the

FIGURE 3 HOW THE SARS-COV-2 VACCINES WORK



BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) are mRNA vaccines. Instructions encoded in mRNA vaccines for SARS-CoV-2 serve as a blueprint for cells to make SARS-CoV-2 spike protein. The mRNA is delivered via lipid nanoparticles, which increase the uptake of the mRNA molecules into cells once an individual is vaccinated. Importantly, the mRNA does not interact with an individual's genetic material or DNA. Once the mRNA is inside the individual's cells, the cellular machinery called ribosome reads the vaccine-derived mRNA as a set of instructions, much like it does for any cellular mRNA, to make the viral spike protein. The immune system sees these protein molecules as foreign invaders, which triggers the activation of the body's defense mechanisms including activation of B and T cells, which further leads to the production of antibodies and memory cells that protect against future SARS-CoV-2 infection. In other words, if the person is exposed to SARS-CoV-2 subsequently, the immune system will recognize it and eliminate any infected cells and the viral particles.

JNJ-78436735 (Janssen) is a viral-vector vaccine, which uses a different approach than the mRNA vaccines but instructs a recipient's cells to make the same SARS-CoV-2 spike protein. The vaccine comprises a harmless (inactivated) form of an adenovirus (virus that causes common colds) which is engineered to carry the genetic code of the SARS-CoV-2 spike protein. Once an individual is vaccinated the code is taken up by the individual's cells and instructs the cells to produce the spike protein, which in turn activates the immune system by creating antibodies and memory cells to protect against an actual SARS-CoV-2 infection.

- Potential therapeutics, including vaccines candidates, go through **three phases of clinical trials** to make sure they are safe and effective for public use.
- Traditionally, the three phases of clinical trials are **performed sequentially**.
- **During the development of COVID-19 vaccines, these phases overlapped** to speed up the process so that the vaccines could be authorized for public use as quickly as possible to control the pandemic. **No trial phases were skipped**.
- COVID-19 vaccine clinical trials involved **tens of thousands of participants of different ages, races, and ethnicities**. Results from these trials have shown that COVID-19 vaccines are effective against infection and severe disease.

TABLE 1 TREATMENTS FOR COVID-19*

Treatment Name	Mode of Action	Approval Status	Indication for Use	Scientific Evidence for EUA/Approval
Bamlanivimab and etesevimab	Antibodies that bind to the SARS-CoV-2 spike protein and block its interaction with the human ACE2 receptor thereby preventing viral attachment to host cells.	EUA**	Mild-to-moderate COVID-19 in adult and pediatric patients (including newborns) with SARS-CoV-2 positive viral test, and at high risk for progression to severe COVID-19.	While this combination therapy is approved for postexposure treatment, the data supporting authorization came from a clinical trial that evaluated bamlanivimab alone for prevention of COVID-19. Those treated with bamlanivimab had a reduced risk (compared to placebo) of being infected with COVID-19. The FDA expects that bamlanivimab and etesevimab together may be safe and effective for postexposure treatment, as bamlanivimab and etesevimab administered together will provide an advantage over bamlanivimab alone against certain SARS-CoV-2 viral variants.
Baricitinib (Olumiant)	By inhibiting the protein Janus kinase (JAK) it blocks signaling mediated by the inflammatory cytokine, IL-6.	EUA	Hospitalized adult and pediatric patients (two years or older) with COVID-19 requiring supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation.	The authorization was supported by data from a clinical trial of hospitalized patients with COVID-19, where baricitinib showed a reduction (compared to standard of care) in the proportion of patients who died during 28 days of follow-up.
Casirivimab and imdevimab (REGEN-COV)	Antibodies that bind to the SARS-CoV-2 spike protein and block its interaction with the human ACE2 receptor thereby preventing viral attachment to host cells.	EUA	Mild-to-moderate COVID-19 in adult and pediatric patients (12 years and older weighing at least 40 kg) with SARS-CoV-2 positive viral test, and at high risk for progression to severe COVID-19.	Most important evidence for authorization came from a clinical trial that showed that the treatment lowered disease progression, hospitalizations, and emergency room visits (compared to placebo) among patients who are at high risk for severe COVID-19.
COVID-19 convalescent plasma (with high antibody levels)	Contains antibodies that can block SARS-CoV-2 attachment to host cells and reduce the amount of virus in the host.	EUA	Hospitalized patients with COVID-19 early in the disease course and those hospitalized patients who have impaired immunity and cannot produce an adequate antibody response. Plasma with low levels of antibodies has not been shown to be helpful in COVID-19.	Based on available scientific evidence the FDA determined that it is reasonable to believe that COVID-19 convalescent plasma may be effective in lessening the severity or shortening the length of COVID-19 illness in some hospitalized patients.
Molnupiravir (Lagevrio)	Blocks viral multiplication by promoting widespread mutations during the replication of viral RNA.	EUA	Mild-to-moderate COVID-19 in adults with SARS-CoV-2 positive viral test who are at high risk for progression to severe COVID-19, for whom alternative treatment options are not accessible or clinically appropriate.	The data supporting this EUA are from the MOVe-OUT clinical trial that showed that only 6.8 percent of COVID-19 patients who received molnupiravir were hospitalized or died compared to 9.7 percent of those who received placebo.

*This table includes therapeutics that have received EUA and/or approval from FDA as of January 1, 2022, for the treatment of COVID-19. Not included are agents that are authorized for managing COVID-19-induced complications (such blood clotting) or for sedating ventilated patients.

**Emergency Use Authorization (EUA) provides faster access to critical medical products that may help during an emergency when there are no adequate, approved, and available options. To issue an EUA, FDA quickly evaluates the evidence that is currently available, carefully balancing the risks and benefits of a product as known at the time, among other criteria.

TABLE 1 TREATMENTS FOR COVID-19* (CONTINUED)

Treatment Name	Mode of Action	Approval Status	Indication for Use	Scientific Evidence for EUA/Approval
Nirmatrelvir and ritonavir (Paxlovid)	Blocks SARS-CoV-2 multiplication by inhibiting the viral protein, nsp5 protease.	EUA**	Mild-to-moderate COVID-19 in adult and pediatric patients (12 years and older weighing at least 40 kg) with SARS-CoV-2 positive viral test, and at high risk for progression to severe COVID-19.	The data supporting this EUA are from the EPIC-HR clinical trial that showed that only 0.8 percent of COVID-19 patients who received Paxlovid were hospitalized or died compared to six percent of those who received placebo.
Remdesivir (Veklury)	An inhibitor of the SARS-CoV-2 protein RNA-dependent RNA polymerase, which is essential for viral replication.	Approved	Adult and pediatric patients (12 years and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization, only to be administered in a hospital or in a health care setting capable of providing acute care comparable to inpatient hospital care.	The approval was supported by the FDA's analysis of data from three clinical trials which showed that treatment with remdesivir either reduced (compared to placebo) time to recovery or increased the odds of symptoms improving among patients hospitalized with mild, moderate, or severe COVID-19.
Sotrovimab (Xevudy)	Antibody that binds to the SARS-CoV-2 spike protein and inhibits viral infection of human cells.	EUA	Mild-to-moderate COVID-19 in adult and pediatric patients (12 years and older weighing at least 40 kg) with SARS-CoV-2 positive viral test, and at high risk for progression to severe COVID-19.	The data supporting the EUA are based on an interim analysis of a clinical trial that showed that progression to severe COVID-19 (hospitalization or death) was reduced in patients treated with sotrovimab compared to those who received placebo.
Tixagevimab and cilgavimab (Evusheld)	Antibodies that bind to the SARS-CoV-2 spike protein and block its interaction with the human ACE2 receptor thereby preventing viral attachment to host cells.	EUA	To prevent COVID-19 in adults and children (12 years and older weighing at least 40 kg) who are not currently infected with SARS-CoV-2 but are immunocompromised and may not mount an adequate immune response to COVID-19 vaccines or for whom vaccination is not recommended due to a history of severe adverse reaction.	Data supporting this EUA came from the PROVENT clinical trial which showed that Evusheld recipients had a 77 percent reduced risk of developing COVID-19 compared to those who received a placebo and the reduction in risk of developing COVID-19 was maintained for six months.
Tocilizumab (Actemra)	Antibody that binds to the receptor of the inflammatory cytokine IL-6 and inhibits IL-6-mediated signaling.	EUA	Hospitalized adult and pediatric patients with COVID-19 (two years and older) who are receiving systemic corticosteroids and require supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation.	The critical evidence on the potential benefit of tocilizumab came from two clinical trials. In the RECOVERY trial, treatment with tocilizumab reduced (compared to usual care) the probability of death and median time to discharge among hospitalized patients with severe COVID-19. In the EMPACTA trial, treatment with tocilizumab reduced (compared to placebo) progression to mechanical ventilation or death.

*This table includes therapeutics that have received EUA and/or approval from FDA as of January 1, 2022, for the treatment of COVID-19. Not included are agents that are authorized for managing COVID-19-induced complications (such blood clotting) or for sedating ventilated patients.

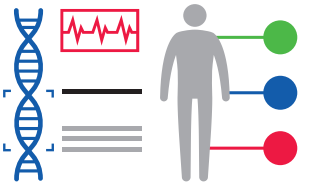
**Emergency Use Authorization (EUA) provides faster access to critical medical products that may help during an emergency when there are no adequate, approved, and available options. To issue an EUA, FDA quickly evaluates the evidence that is currently available, carefully balancing the risks and benefits of a product as known at the time, among other criteria.

United States until December 2021 (130,139-141). Researchers anticipate that with time, additional SARS-CoV-2 VOC will arise. As a recent example, on November 26, 2021, a new variant first reported out of South Africa (Omicron) was classified as a VOC by the WHO (51). Omicron variant was soon detected in the U.S. and as of January 1, 2022, it was estimated to make up more than 95 percent of the COVID-19 variants circulating in the United States (138). Ongoing and future studies will need to investigate how long the vaccines are effective, the impact of the variants on vaccine effectiveness, and whether it is necessary to administer additional doses or develop new vaccines that more closely reflect the circulating virus variants at the time (142-144). Of note, as of January 2022, there are 276 vaccines in various stages of development globally, of which 108 are in clinical testing (145).

Despite the knowledge that COVID-19 vaccines are safe and effective, uptake of vaccination has been suboptimal in the United States. As of January 2022, only about 63 percent of the U.S. population has been fully vaccinated. There are also stark disparities in the uptake of vaccination. For instance, among insured U.S. individuals age 16 and older, the receipt of one or more doses was lower among those who are non-Hispanic Black (41 percent) and Hispanic (41 percent) compared to those who are non-Hispanic white (55 percent); coverage was highest (57 percent) among non-Hispanic Asian individuals (146). A study that examined data from the nine largest U.S. cities found that, in neighborhoods with the lowest vaccination rates, 25 percent of the population was Black, and 52 percent was white, while in neighborhoods with the highest vaccination rates, only six percent of the population was Black while 70 percent was white (147). The average low-vaccination neighborhood had half the median income and over twice the poverty rate of the average high-vaccination neighborhood (147). COVID-19 vaccination coverage has also been lower in rural counties (39 percent) compared to urban counties (46 percent) (148). Taken together, these data are especially concerning because the same populations in which the uptake of COVID-19 vaccines is particularly low are also the ones that have shouldered the greatest burden of the pandemic (149). Public health interventions at local, state, and federal levels are needed to raise awareness and education around the vital importance of COVID-19 vaccination to ensure equitable uptake in communities that have been hardest hit by the pandemic.

Patients with cancer were not included in the original clinical trials that tested the safety and efficacy of the currently authorized COVID-19 vaccines in the U.S. However, real-world evidence gathered since the EUA and/or approval of COVID-19 vaccines has indicated that they are effective and elicit anti-SARS-CoV-2 immune responses in patients with cancer (150,151) (see **Prevention and Treatment of COVID-19 in Patients with Cancer**, p. 47). However, because many patients with cancer are immunocompromised due to their disease and/or the treatments received, the immune responses generated in this vulnerable population may be weaker and may last for a shorter period of time compared to healthy immunocompetent individuals (152-154). Therefore, FDA and CDC recommend that patients with cancer receive additional doses of the vaccine for optimal protection against COVID-19 (see **Prevention and Treatment of COVID-19 in Patients with Cancer**, p. 47).

FDA defines **real-world data** as **data relating to patient health status** and/or the **delivery of health care** routinely collected from a variety of sources and real-world evidence as the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real-world data.



TREATMENTS FOR COVID-19

Infection with SARS-CoV-2 causes a wide range of symptoms and disease severity. More than 80 percent of people who are diagnosed with COVID-19 have mild symptoms and do not require hospitalization (83,155). Among those patients who require hospitalization, fewer than 30 percent have critical disease and require admission to the intensive care unit (156). Several treatments are available for COVID-19 patients who have mild to moderate symptoms, for those who are hospitalized, and for individuals who may be asymptomatic but are at high risk for serious COVID-19 and have been exposed to someone who has tested positive for COVID-19. It should be noted that randomized, double-blind, placebo-controlled clinical trials are the most rigorous and reliable ways to find successful treatments for diseases including COVID-19. In these trials, participants are assigned randomly to receive either the drug being tested, or a placebo—a treatment that has none of the active drug in it. To remove any bias, both health care providers and participants are kept unaware (double-blind) of which intervention the participants have received until the trial is over.

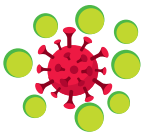
NIH has provided specific guidelines for clinical management of COVID-19 depending on the symptoms, susceptibility of a patient for severe COVID-19, and whether a patient is being cared for at home or at the hospital (157). Patients with mild COVID-19 symptoms who are being cared for at home are recommended over-the-counter medicines, such as

Emergency Use Authorization (EUA)

EUA provides faster access to critical medical products that may help during an emergency when there are no adequate, approved, and available options. To issue an EUA, FDA quickly evaluates the evidence that is currently available, carefully balancing the risks and benefits of a product as known at the time, among other criteria.

WHAT TYPES OF TREATMENT ARE BEING INVESTIGATED FOR COVID-19?

Several types of therapeutics are being investigated in clinical trials as potential treatments for COVID-19. These include:

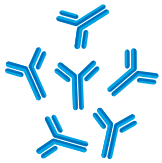


Antiviral therapeutics

These therapeutics directly target SARS-CoV-2, preventing virus infection and spread, for example, 4'-fluorouridine.

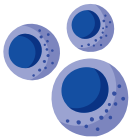
Immunomodulators

These therapeutics are designed either to boost the immune system (for people who cannot mount an adequate defense against COVID-19), for example, interferon beta; or to dampen the patient's abnormal immune response following infection with SARS-CoV-2, for example, infliximab or colchicine.



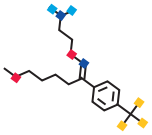
Neutralizing antibody therapies

These treatments include manufactured antibodies, for example, AZD7442; animal-sourced antibody therapies; and blood-derived products such as convalescent plasma and intravenous immunoglobulin (IVIG), which contain antibodies taken from people who have previously had COVID-19. The aim of these treatments is to reduce the level of virus shortly after infection and thereby protect against severe disease. Such antibodies could also be used to prevent SARS-CoV-2 infection in those known to be at high risk.



Cell therapies

These treatments include cellular immunotherapies such as engineered Natural Killer (NK) cells and other types of cells, and related products, for example mesenchymal stem cells. They work to combat COVID-19 in a variety of ways (168-170).



Others

Numerous other agents that work through various mechanisms are being tested against COVID-19. These include treatments that are already approved for other diseases such as cancer (e.g., bicalutamide or enzalutamide), neuropsychiatric illness (e.g., the antidepressant fluvoxamine), among others.

It is noteworthy that the potential benefit of these treatment approaches is currently under investigation in clinical trials and health care experts may recommend against the use of these agents for the treatment of COVID-19, except in a clinical trial setting. It is important that patients with COVID-19 speak with their health care providers to decide the best treatment option.

acetaminophen, to relieve their symptoms. FDA has issued EUAs for three treatments for patients who are at home with mild or moderate symptoms or are asymptomatic but are at a high risk for progressing to severe disease due to exposure to someone with COVID-19 (see **Table 1**, p. 30) (158). These treatments comprise antibodies that attach to SARS-CoV-2 and help the immune system recognize and eliminate the virus. By reducing the amount of virus in the body the antibodies decrease the likelihood of a patient progressing to severe disease.

Additional treatment options have been approved or authorized for emergency use by FDA for hospitalized COVID-19 patients with serious illness (see **Table 1**, p. 30). These include antivirals—therapeutics that block viral multiplication and spread in the body—and convalescent plasma—blood plasma from patients who have recovered from COVID-19—which contain SARS-CoV-2 antibodies that help the immune system recognize and eliminate the virus. Furthermore, FDA has issued EUAs for treatments that are aimed to mitigate the overactive immune response as well as certain other pulmonary or cardiovascular complications associated with severe COVID-19. Of note, investigations are still ongoing to yield definitive evidence of clinical benefit for some of these treatments (159).

Researchers are also evaluating the benefit of these therapeutics at different stages of disease beyond what has been already approved and/or authorized (160).

In addition to the treatments that received EUA and/or full approval by FDA, there are numerous other therapeutics at various stages of clinical testing as potential treatments for COVID-19 (159,161-163). A wide range of agents, including antivirals, anti-inflammatory drugs, and immune-system modulators, are being investigated in large, international, cross-sector, multi-institutional clinical trials such as Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV), Randomized Evaluation of COVID-19 Therapy (RECOVERY), and the WHO SOLIDARITY PLUS, among others (see sidebar on **What Types of Treatment Are Being Investigated for COVID-19?**, p. 33) (164-166). One area of active research is the repurposing of therapeutics that are already under investigation or have been approved by FDA for other diseases, including cancer, for use in COVID-19 because we already have information about dosage, toxicity, and adverse effects for these therapeutics which can accelerate the pace of development and approval relative to the development of novel therapeutics (167,168).

Because patients with cancer are especially susceptible to severe COVID-19 (see **Burden of COVID-19 in Patients with Cancer**, p. 41), it is vitally important that researchers investigate the safety and efficacy of COVID-19 treatments in this vulnerable population. The fact that the compromised immune system in many cancer patients allows for persistent infection, together with new evidence of novel mechanisms of immune evasion and SARS-CoV-2 variant emergence induced by certain treatments (171), necessitates that health care providers carry out comprehensive ongoing clinical and virological follow-up of these patients.

CANCER RESEARCHERS WORKING TO COMBAT THE COVID-19 PANDEMIC

In this section, you will learn:

- Cancer researchers were uniquely positioned to respond to the many challenges posed by COVID-19 and have played a vital role in combating the public health crisis while continuing their quest to prevent and cure cancer.
- Since the onset of the pandemic, NCI has launched many cross-cutting efforts to investigate the epidemiology of COVID-19 burden, immune responses to SARS-CoV-2 and vaccines and their impact on disease development and severity, modifiable risk factors, and genetic and immune biomarkers of severe COVID-19, among other studies.
- Scientific discoveries and technological innovations in cancer science and medicine have helped with understanding and addressing COVID-19.
- Decades of research into mRNA vaccines for cancer immunotherapy paved the way for the development of SARS-CoV-2 vaccines at an unprecedented speed.

Cancer researchers were uniquely positioned to respond to many of the challenges posed by COVID-19, and many refocused their expertise to combat the unprecedented global pandemic (172). Extensive experience in genetics, epigenetics, immunology, and drug development, among other scientific and clinical areas, made cancer scientists well suited to investigate COVID-19 biology and therapeutics. Furthermore, cutting-edge technologies, for example, next-generation sequencing (NGS), which is routinely used in cancer research to uncover the wide range of genetic alterations within subsets of cancer cells that drive tumor growth, were repurposed effectively to characterize the genomic sequence of SARS-CoV-2 and identify novel variants of SARS-CoV-2 (see **Figure 4**, p. 38). Genomic sequencing using NGS technology allowed public health experts and researchers to track the transmission of SARS-CoV-2 globally, detect mutations rapidly to prevent the spread of new variants, and identify mutations that can evade detection by established diagnostic assays, or that can affect vaccine potency.

NCI lent its substantive expertise and cutting-edge resources to conduct research that continues to contribute to the global effort to address COVID-19 (173) (see **Table 2**, p. 36). Since the onset of the pandemic, NCI has launched many cross-cutting efforts that involve all stakeholders in the medical research community. The many areas that are being investigated by cancer scientists include epidemiological analyses of trends in COVID-19 mortality, immune responses to SARS-CoV-2 and vaccines and their impact on disease development and severity, genetic and immune biomarkers of severe or fatal COVID-19, and modifiable risk factors for COVID-19 severity.

Cancer researchers are also monitoring the short- and long-term impact of COVID-19 on patients with cancer. One area in which cancer researchers have vast expertise is the integration, analysis, and sharing of large and complex datasets, also known as "big data." This expertise is being harnessed to better understand the effects of COVID-19 on patients with cancer. The goal is to obtain clinical and other patient-related information on a large scale to answer questions about the epidemiology of COVID-19 in patients with cancer, as well as the effectiveness of COVID-19 diagnostics, vaccines, and treatments in cancer patients. Several cancer organizations as well as multi-institutional teams have already launched initiatives to catalyze data sharing (see **Table 3**, p. 45).

STUDYING THE IMMUNE RESPONSE TO SARS-COV-2 AND COVID-19 VACCINES

Understanding how the immune system responds to both SARS-CoV-2 and COVID-19 vaccines is key to managing community spread and developing treatments. Serology tests measure an individual's immune response to an infection in the form of antibodies in the blood and are integral to our understanding of the prevalence of COVID-19 and SARS-CoV-2 immune response (see sidebars on **How Can We Test for SARS-CoV-2?**, p. 26, and **How Is the Immune Response to COVID-19 Vaccines Evaluated?**, p. 49). NCI has the HPV Serology Laboratory, a world-class serology facility that works to standardize human papillomavirus (HPV) antibody testing. Emergency appropriations by Congress in April 2020 provided NCI with additional resources to develop,

TABLE 2 SELECTED COVID-19 RESEARCH INITIATIVES AT NCI*

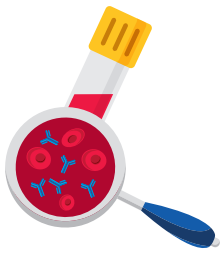
NCI Initiative	Goals of the Initiative
Serological Sciences Network (SeroNet)	Support research on the immune response to SARS-CoV-2 and its impact on COVID-19 development and severity, as well as increase the nation's serological testing capacity.
NCI COVID-19 in Cancer Patients Study (NCCAPS)	Clinical investigation of patients with cancer who have COVID-19. The study aims to enroll more than 2,000 patients of all ages, collect comprehensive data on their cancer types, treatments received, symptoms, etc., and follow them for an extended period of time to better understand the effects of SARS-CoV-2 on people with cancer.
COVIDcode Study	A collaboration with the National Human Genome Research Institute and the National Institute of Allergy and Infectious Diseases to learn more about the genetic and immunologic contributions to the severity of COVID-19.
COVNET	A large genome-wide association study to identify common and rare germline genetic variants associated with susceptibility to severe or fatal COVID-19 disease.
COVID-19 and Cancer Linkage (COVCan) Study	Link data from several state cancer registries and COVID-19 surveillance systems. The study will allow investigators to assess the risk of COVID-19 hospitalization and death among cancer patients and survivors, as well as identify patient characteristics and cancer sites exhibiting the strongest associations with severe COVID-19.
COVID-Mortality Tracker	A collaboration of epidemiologists and data scientists to monitor weekly U.S. trends in overall and cause-specific mortality since the onset of the pandemic.
COV2Base Study	To examine the effect of SARS-CoV-2 infection on patients with rare diseases (e.g., Li-Fraumeni syndrome, DICER1 syndrome), quantifying the frequency and severity and looking for conditions that increase risk of severe outcomes. Additionally, this project will work to identify biological or sociodemographic characteristics that increase risk of severe COVID outcomes that may inform future genetic modifier studies.
COVID-19 Seroprevalence Studies Hub (SeroHub)	Compare COVID-19 seroprevalence studies across the country.

*Many of these initiatives are being led in collaboration with other institutes at NIH or other federal organizations.

validate, improve, and implement serology testing and associated technologies to respond to the pandemic. Soon thereafter, NCI unified its national network of serology centers, including the HPV Serology Laboratory and others, and created the Serological Sciences Network (SeroNet) to support research on SARS-CoV-2 immunology and to increase the nation's serological testing capacity. Research investigations as part of SeroNet aim to answer critical questions such as the underlying causes of differential symptoms among COVID-19 patients, prevalence of SARS-CoV-2 infection among different U.S. demographic groups, incidence of SARS-CoV-2 reinfection, cellular and molecular markers of COVID-19 immunity, and genetic and environmental factors that affect immune response, among others (174).

Investigators who are part of the SeroNet initiative collaborated with FDA and CDC to validate SARS-CoV-2 antibody tests submitted to FDA (see sidebar on **How Can We Test for SARS-CoV-2?**, p. 26). The goal was to ensure that the tests made available to the public are accurate and reliable. A key question vital for our understanding of the immunity against SARS-CoV-2 is whether a certain level of SAR-CoV-2 antibodies is needed for protection from a future infection. By following vaccinated individuals, as well as COVID-19 patients over time, SeroNet researchers aim to determine the antibody levels that correlate with protection from severe disease.

SeroNet is supporting basic and applied serological research related to COVID-19 at 13 universities, eight Serological Sciences Centers of Excellence, four Serological Sciences Network Capacity Building Centers, the HPV Serology Laboratory at the Frederick National Laboratory for Cancer Research (FNLCR), and a coordinating center at FNLCR (173).



One of the challenges in quantifying antibody correlates for protection from COVID-19 across a large population is that different research groups use different methods to measure antibody levels, which makes comparison between groups difficult. Scientists at SeroNet have addressed this issue by developing a benchmark SARS-CoV-2 serology standard, which allows research teams to compare antibody levels across different studies, even if they have used different serology tests. Notably, researchers at NCI have now calibrated the serology standard to a unit of measure that is approved by WHO and can be compared across international studies. In collaboration with the National Institute of Allergy and Infectious Diseases (NIAID) and CDC, NCI has also developed and implemented an online dashboard, SeroHub, which catalogs data on the percentage of people who were infected during a certain time, called seroprevalence, so that scientists and policy makers can make evidence-based decisions on public health.

Research from NCI's SeroNet has uncovered important insights into the mechanisms of immune response to COVID-19. These studies include comparisons between immune responses from natural infection with SARS-CoV-2 and immune responses achieved through the vaccines (175,176). Others have examined the immune response achieved through COVID-19 vaccines to the newer variants of SARS-CoV-2 or among vulnerable populations, such as patients with cancer. Results from these studies indicate that the vaccines may be less effective in certain cancer patients but, encouragingly, the reduced immunity conferred by all three COVID-19 vaccines in this vulnerable population is retained against the various newer variants of the virus (177-180). These data have been critical for public health experts at CDC for making important decisions, such as whether additional primary doses or boosters of the COVID-19 vaccine are needed for the general population and for vulnerable groups that include patients with cancer, and to determine the optimal time frame for administering additional doses.

USING LESSONS LEARNED FROM CANCER TO UNDERSTAND SARS-COV-2 BIOLOGY

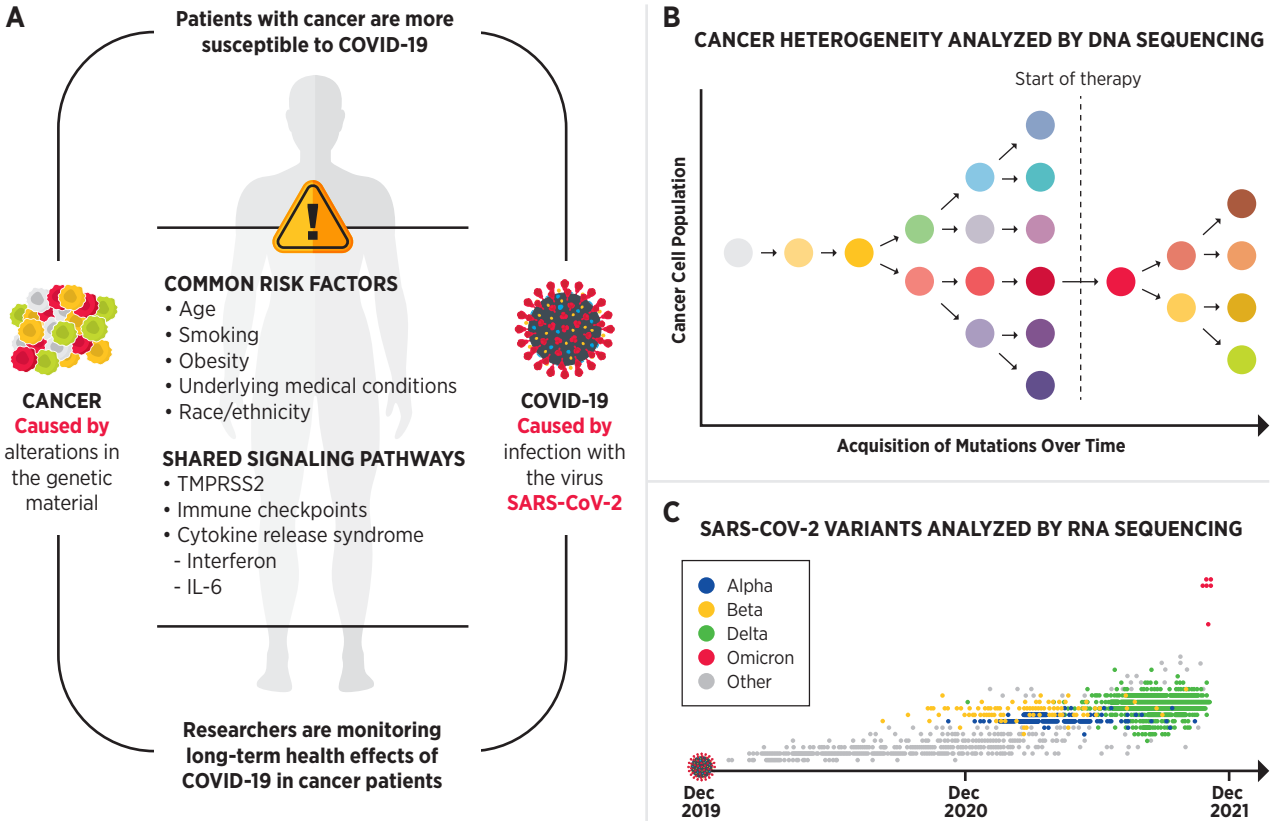
While the COVID-19 pandemic presented unprecedented challenges to the entire medical research community, it also emphasized the vital importance of investments in medical research including in basic research. Scientific discoveries that resulted from decades of research funding and work across many disciplines including cancer biology were rapidly harnessed to address the numerous clinical questions posed by COVID-19. In fact, critical insights into the biology of SARS-CoV-2 and the pathology of COVID-19, which led to rapid advances in the development of vaccines and potential treatments, were derived from the knowledge obtained from cancer science and medicine. Two areas where researchers have drawn knowledge from cancer biology are the mechanism by which SARS-CoV-2 enters the host cell and the immune response to COVID-19 (see **Figure 4**, p. 38).

Coronaviruses, including SARS-CoV-2, rely on the host protein TMPRSS2 for entry into human cells (see **Figure 2**, p. 15).

Many of the insights related to TMPRSS2 protein expression and function have come from cancer research. TMPRSS2 was initially identified in prostate cancer and its gene is known to be highly upregulated in prostate cancer cells (40,41). It is also known that the levels of TMPRSS2 in the healthy prostate tissue, as well as in prostate cancer, are regulated by the male hormone androgen and its receptor (13,40,41). Studies have recently shown that TMPRSS2 is also expressed in the lungs, the main conduit for COVID-19 (13). Ongoing research is investigating whether TMPRSS2 levels in the lungs are also regulated by androgen, as is the case in prostate tissue, and whether males have a higher abundance of TMPRSS2 proteins compared to females (41). Data from this line of research can provide valuable insights into the predominance of COVID-19 severity and death in men. A subsequent question is whether it is possible to reduce the susceptibility to SARS-CoV-2 infection, COVID-19 pulmonary symptoms, and severe disease by targeting TMPRSS2, such as by inhibiting the levels of androgen through androgen deprivation therapies (ADT), a mainstay in the treatment of prostate cancer. At the onset of the COVID-19 outbreak, a retrospective analysis from Italy found that while men generally had worse outcomes from COVID-19, prostate cancer patients treated by ADT were less likely to be infected with SARS-CoV-2 compared to patients who were not on the therapy or patients with other types of cancers (181). Similarly, a second retrospective analysis in the United States showed that prostate cancer patients treated with ADTs were less likely to develop adverse clinical outcomes compared to those not on this regimen (182). While emerging data from more recent studies do not support an association between ADT and COVID-19 mortality (183), additional ongoing clinical trials are seeking definitive answers to whether there are any potential benefits of ADTs in mitigating the symptoms of COVID-19 and are evaluating a range of TMPRSS2-targeted therapeutics that either lower its expression level or inhibit its function (23).

Immunotherapy is another area of cancer science and medicine that has contributed critical elements to our understanding of COVID-19 and to addressing the most severe symptoms associated with it. Immunotherapeutics work by unleashing the power of a patient's immune system to fight cancer the way it fights pathogens such as the flu virus or the bacterium that causes strep throat. The use of immunotherapeutics in the treatment of cancer is referred to as cancer immunotherapy. In the past decade, it has revolutionized the treatment of an increasingly broad array of cancer types (38). One type of cancer immunotherapy called CAR T-cell therapy works by amplifying the killing power of the immune system by providing more cancer-targeted immune cells called T cells (see sidebars on **Key Cells in the Immune System**, p. 17, and **What Are Cancer Immunotherapies and How Do They Work?**, p. 19). CAR T-cell therapy was first approved by FDA in 2017 for the treatment of children and young adults with a certain type of leukemia (184). Researchers who were involved with the development of CAR T-cell therapy noticed that the treatment could potentially have certain adverse effects, some of which were very severe and, in some cases, life-threatening. One of the most concerning was a phenomenon known as cytokine release syndrome (CRS). During CAR T-cell therapy, CRS occurs when the engineered T cells attack cancer cells and release chemicals called cytokines (for example, interleukin-6 or IL-6) that can help in the eradication of cancer. However, in patients affected by CRS, such

FIGURE 4 LESSONS FROM CANCER RESEARCH HELPED ADDRESS COVID-19



A. Knowledge derived from decades of cancer research has helped the medical research community respond to many of the challenges posed by COVID-19. It became evident quite early in the pandemic that there were parallels between COVID-19 and cancer. For example, several risk factors such as advanced age, smoking, and obesity, and certain underlying medical conditions increase risk for both diseases. In addition, researchers identified common cellular and molecular markers that are associated with the etiology and/or pathology of both diseases. These include the cell surface protein TMPRSS2 which has been long associated with prostate cancer and was also found to facilitate SARS-CoV-2 entry into human cells. Research discoveries in cancer immunology, e.g., how the immune system responds to cancer cells, and mechanisms deployed by tumors to evade the immune system, such as checkpoint inhibitors, have provided key insights into the immune response to COVID-19. Furthermore, cytokine release syndrome, a phenomenon mediated by an abnormal activation of the immune system observed in patients with cancer treated with certain immunotherapeutics, also occurs in patients with severe COVID-19. These shared pathways between cancer and COVID-19 have allowed cancer researchers to evaluate the efficacy of several anticancer therapeutics for the treatment of COVID-19.

B. Beyond scientific discoveries, state-of-the-art technologies that are used to answer cancer's most elusive questions are now aiding public health experts to mitigate the spread of the pandemic. As one example, next-generation sequencing (NGS) is a comprehensive method for assessing the genetic alterations associated with tumors. The technology allows researchers to capture tumor heterogeneity—diversity in genetic alterations among different cancer cells within a tumor as between primary and metastatic tumors—and track these changes over time. The data provide insights on the chronology of tumor evolution and identify how cancer therapeutics might influence intratumor heterogeneity.

C. NGS technology has also played a pivotal role in addressing the SARS-CoV-2 pandemic. It has helped public health researchers sequence thousands of SARS-CoV-2 genomes worldwide, enabling a better understanding of the spread and evolution of the virus. Notably, NGS has been indispensable for tracing the emergence of new SARS-CoV-2 variants and using this information to better guide public health.

Adapted from (184a,184b).

as **Larry Saltzman, MD** (see p. 52) who experienced two episodes of CRS following CAR T-cell therapy, there is an overwhelming release of cytokines into the bloodstream, which can cause high fevers, flu-like symptoms, and a dramatic drop in blood pressure. For many patients, treatment with steroids can relieve the CRS. However, others require treatment with tocilizumab (Actemra), which blocks IL-6, and was approved to treat severe or life-threatening CRS caused by CAR T-cell therapy in 2017.

Notably, severe COVID-19 is associated with an increase in proinflammatory cytokines and an overactive immune response which is similar to what is observed after CAR T-cell therapy (185,186). Inflammation in the lungs can progress to acute respiratory distress syndrome (ARDS), causing difficulty breathing and low blood oxygen levels. If unchecked, ARDS can progress to respiratory failure, which is the cause of death in many fatal COVID-19 cases. In addition, uncontrolled CRS may lead to failure of other organs, most notably the heart, liver, and kidneys. Although there may be certain differences in the underlying biology between inflammatory responses in cancer and in COVID-19, many of the same cytokines, such as IL-6, are involved in both phenomena. Researchers have utilized the knowledge learned in cancer to identify cytokine biomarkers that are indicative of severe COVID-19 and to investigate therapeutic options to mitigate CRS among severely ill COVID-19 patients (23,168,186,187). These approaches include clinical studies on "repurposing" tocilizumab and other IL-6 inhibitors to slow and reduce inflammation in COVID-19 patients with CRS (see **Repurposing Anticancer Agents to Treat COVID-19**, p. 40) (168).

Beyond the management of CRS, cancer researchers have provided their scientific and technological expertise from immune profiling in cancer research to characterize key aspects of the immune response to SARS-CoV-2 (188). As one example, cancer researchers adapted tests that they routinely use to monitor T-cell responses to tumor proteins for studies of the coronavirus to determine how T cells are activated in response to certain viral proteins, such as the SARS-CoV-2 spike protein. These tests can determine whether COVID-19 vaccines can elicit effective immune responses especially in cancer patients undergoing treatment.

DEVELOPING COVID-19 VACCINES

The successful development of several safe and effective COVID-19 vaccines in an unprecedentedly short time was made possible due to the rapid mobilization of the global medical research community and concerted efforts from all stakeholders including the government and private sectors. It should be noted that the path to successful mRNA vaccines drew on extensive research in cancer science and medicine (131,189). For decades, scientists have studied how to use mRNA to help the immune system fight cancer. While the development of effective mRNA-based cancer vaccines has proven challenging because of the complexities of cancer—a collection of more than 200 diseases (190), the incremental progress in understanding the science and refining the technology has contributed tremendously to the rapid development of the COVID-19 vaccines. Beyond mRNA vaccines, many other COVID-19 vaccine candidates built around inactivated viruses, viral vectors, or engineered viral proteins that are currently being evaluated, feature design elements informed by prior cancer therapy efforts (189,191,192).

The mRNA vaccine platform was developed and tested for cancer, albeit as an experimental therapeutic rather than a preventive agent. Genetic mutations that lead to cancer leave their signature in various altered proteins (see sidebar on **Genetic Mutations**, p. 18). Therefore, the aim was to create mRNAs that encode the altered proteins—called tumor antigens or neoantigens—that are expressed in cancer cells and contribute to their malfunction. When injected into a patient, these mRNAs generate the tumor antigens or neoantigens, which flag the cancer cell for destruction by the immune system. It should be noted that the tumor antigens may look very different in different patients, which necessitates sampling of each patient's tumor and characterizing the mutations to develop personalized vaccines that are specific to individual patients.

For more than 25 years, cancer researchers have been refining the science and technology of mRNA vaccination by evaluating potential routes of mRNA administration as well as various delivery methods to identify the best way to elicit optimal immune responses (193). Among the delivery approaches that have been tested include isolating immune cells known as dendritic cells from the blood (see sidebar on **Key Cells in the Immune System**, p. 17), modifying them by introducing an mRNA that encodes tumor antigen, and injecting them back into the cancer patient where these cells would trigger cancer-fighting T cells to attack and eliminate tumors (189). Additionally, extensive research has been done to identify ways to increase the efficiency of mRNA delivery, e.g., the use of lipid-based delivery systems, much like the lipid nanoparticle formulation that was used for the COVID-19 vaccines. Furthermore, while researchers are monitoring the long-term health of individuals who have received the new SARS-CoV-2 mRNA vaccines, it should be noted that preclinical and clinical studies in cancer have thus far established the feasibility and safety of this approach (194).

Notably, a key consideration for the development of clinically useful personalized mRNA-based cancer vaccines is the time it takes to develop these agents. For cancer patients in clinical trials, time is of the essence. The expertise to generate a personalized cancer vaccine rapidly for each new patient has served as an advantage for developing the COVID-19 vaccine. It took less than two months from the time the SARS-CoV-2 genome sequence was determined to begin human testing of the mRNA vaccines (131). Research tools that were previously used to predict which parts of mutated tumor proteins make the best targets for immune activation were repurposed to identify specific parts of SARS-CoV-2 proteins that could be encoded in mRNA vaccines for optimal immune responses (192).

As SARS-CoV-2 variants with novel mutations are continuing to emerge across the globe, the versatility and speed of the mRNA vaccine development ensure that these vaccines can be quickly modified to target the newer viral strains. In fact, researchers believe that, in the same manner in which cancer vaccines can be generated against novel tumor-specific proteins within months, new mutations in SARS-CoV-2

Selected Examples of mRNA Vaccine Research in Cancer (189,193)

1995 – mRNA tested as a cancer vaccine in mice

1996 – Dendritic cells as a delivery method for RNA vaccine showed antitumor effect in mice

2002 – First clinical trial using dendritic cells containing mRNA against prostate cancer

2009 – Direct injection of mRNA tested for melanoma treatment

2017 – First human testing of personalized mRNA cancer vaccines began by Moderna

proteins could be incorporated into future COVID-19 vaccines in a short time. Beyond the scientific and technological expertise generated in cancer research, the unprecedented pace of COVID-19 vaccine development was also made possible because of a robust manufacturing infrastructure that was already in place to develop anticancer products. Taken together, this evidence emphasizes how decades of ongoing efforts in cancer medicine have contributed strongly to the key innovations that led to the design and implementation of the mRNA-based COVID-19 vaccines. Notably, given the global spotlight on the tremendous success of the COVID-19 vaccines, there has been increased enthusiasm for mRNA-based cancer immunotherapies, and many cancer scientists are refocusing on developing mRNA vaccines to fight cancer. Researchers believe that the next wave of breakthroughs in mRNA technologies will revolutionize the landscape of cancer vaccines.

REPURPOSING ANTICANCER AGENTS TO TREAT COVID-19

Over the last decade, oncology has emerged as one of the most exciting areas of drug development. A wide range of agents with diverse mechanisms of action is being evaluated, reviewed, and approved by FDA each year, many of which have been chronicled in the annual *AACR Cancer Progress Report* over the last 11 years (195). Building on the deep scientific knowledge gained from experience in cancer, researchers around the world have worked together to accelerate the SARS-CoV-2 therapeutic development. One area of particular interest is to repurpose treatments used in cancer care for the benefit of patients with COVID-19. Ongoing investigations in cancer drug repurposing are focused mainly on two areas: identifying existing drugs that may target the mechanisms of SARS-CoV-2 entry into the host cell and viral replication; and identifying those that mitigate the overactive immune response seen in patients with severe disease (167,168,196). Although definitive evidence of clinical benefit is still lacking, data from these studies suggest that clinical trials for hypothesis testing of anticancer therapeutics are an encouraging strategy for discovering potential new treatments for COVID-19.

An effective immune response against SARS-CoV-2 depends on the proper activation of T cells, which can eradicate virus-infected cells. It has been shown that patients with severe COVID-19 have reduced numbers of T cells and that the existing T cells exhibit an exhausted characteristic. Cancer immunotherapeutics such as immune checkpoint inhibitors release certain brakes on exhausted T cells, thereby unleashing their ability to eradicate tumors or virus-infected cells. Researchers are therefore examining the potential of checkpoint inhibitors early in the disease (prior to any signs of CRS) in mitigating COVID-19 (197). Ongoing studies are carefully examining in which patient populations and at what stage of the disease these treatments could be used to achieve the best outcomes for patients with COVID-19 (168,197).

One of the most severe symptoms for patients with COVID-19 is an overactive immune system leading to CRS. This can lead to potentially life-threatening complications in the lungs, heart, and other major organs. Scientists are exploring whether anticancer treatments that are known to target inflammation-inducing pathways can be used to slow this overactive immune response in COVID-19 patients. The different classes of therapeutics that are being explored for repurposing include corticosteroids, Bruton tyrosine kinase (BTK) inhibitors such as acalabrutinib and ibrutinib, and JAK/STAT inhibitors such as ruxolitinib, all of which are common treatments for hematologic cancers (170,200). In addition, many research teams are evaluating inhibitors of the cytokine IL-6 for patients with severe COVID-19 (199-201).

Based on the observation that COVID-19 is associated with abnormal blood vessels which may lead to low blood oxygen, morbidity, and mortality, cancer researchers are repurposing antiangiogenic therapeutics used in cancer to treat the vascular defects in COVID-19 (168,202). It should be noted that abnormal vasculature and poor oxygenation are also hallmarks of solid tumors.

There are efforts to identify approved anticancer agents that can block SARS-CoV-2 entry and its multiplication in human cells. As described earlier in the report, proteins ACE2 and TMPRSS2, expressed on the cell surface in the human respiratory tract among other organs, are involved in SARS-CoV-2 entry and infection. TMPRSS2 levels are elevated in prostate cancer cells and regulated by the male hormone androgen, which led to clinical trials testing antiandrogenic therapeutics that are commonly used in prostate cancer in patients with COVID-19 (40,203). While currently available data from these trials remain inconclusive, there are continued efforts to evaluate the clinical benefits of targeting TMPRSS2 levels and/or function in patients with COVID-19 (168). Beyond TMPRSS2, molecularly targeted anticancer therapeutics against several other host proteins that are involved in cellular multiplication and/or survival are being investigated in the context of COVID-19 (167,168,197).

CANCER IN THE MIDST OF COVID-19 AND BEYOND

In this section, you will learn:

- Patients with cancer have a significantly higher risk of COVID-19 infection, severe disease, and death compared to individuals without cancer.
- Patients with blood and lung cancers, and those on active anticancer treatments, are more vulnerable compared to patients with other types of cancers, or those who are not on active anticancer treatments.
- COVID-19 vaccines are effective in patients with cancer, with few to no side effects. Certain patients with blood cancers, who are receiving specific types of treatments, respond to the vaccines to a lesser extent because of the nature of their cancer and the treatment.
- COVID-19 led to closures of research laboratories, resulted in a pause in clinical trials, negatively impacted career development opportunities for the science, technology, engineering and mathematics (STEM) workforce, especially women and minority early-stage investigators, and caused a burnout among health care workers.
- The pandemic disrupted patient care, with a sharp decline in cancer screening, delays or cancellation of cancer treatments, and a negative impact on the mental and psychosocial health of cancer survivors. It also widened cancer health disparities.
- Some aspects of cancer research and patient care, e.g., clinical trials testing new therapeutics, are returning to prepandemic levels. However, the full impact of the disruptions, such as missed cancer screenings during the pandemic potentially leading to an increase in advanced-stage cancer diagnoses, will only become clear in the coming years.

It is increasingly evident that cancer is an independent risk factor for adverse outcomes and mortality in patients with COVID-19 (20,204-209). In a study of more than 73 million patients in the U.S., the risk of COVID-19 infection was seven times higher in patients diagnosed with cancer in the past year, when compared to those with no history of cancer (210). The study also found that mortality in COVID-19 patients with cancer was significantly higher (almost 15 percent) than that in COVID-19 patients without cancer (five percent), or cancer patients without COVID-19 (four percent) (see also sidebar on **COVID-19 in Patients with Cancer**, p. 42) (210). Another recent study involving more than 195,000 COVID-19 patients found that mortality rates decreased in patients with no history of cancer between January and August of 2021, but not in patients with a history of cancer. The study also found that mortality rates were highest among patients who were being actively treated for their cancer (211) (see **Patients with Cancer on Active Anticancer Treatment**, p. 47). These studies, as well as others discussed in this chapter, have established patients with cancer as highly vulnerable to adverse outcomes from COVID-19.

BURDEN OF COVID-19 IN PATIENTS WITH CANCER

Several factors, such as advanced age, that contribute to the development of cancer also appear to increase the risk of severe COVID-19, as well as the overall adverse clinical outcomes from COVID-19 in patients with cancer (see **Figure 5**, p. 43) (217). These risk factors weaken the immune system, making patients with cancer more susceptible to infectious agents, including infections from SARS-CoV-2 (218) (see sidebar on **Why Are Cancer Patients at an Increased Risk of Infection?**, p. 44), and increasing the likelihood of death.

Studies examining the immune system in patients with cancer who have contracted COVID-19 are providing valuable insights into the role of different types of cancer and anticancer treatments in increasing the risk of death in this population. As one example, initial findings from an ongoing study—COVID-19 antiviral response in a pan-tumor immune monitoring, or CAPTURE

COVID-19 IN PATIENTS WITH CANCER

Patients with cancer are highly vulnerable to COVID-19, and this vulnerability is determined by the type of cancer they have and whether they are under active anticancer treatment. The disproportionate burden of COVID-19 in cancer patients is even more pronounced among those belonging to racial or ethnic minorities and other medically underserved populations. Listed below are some recent examples highlighting the multifaceted impact of COVID-19 on patients with cancer:

47% vs 24%	The **hospitalization rates for COVID-19 patients with cancer** were higher than for COVID-19 patients without cancer, 47 percent versus 24 percent (210).
28% vs 16%	**Twenty-eight-day mortality rate in cancer patients with COVID-19** was higher than in cancer patients without COVID-19, 28 percent versus 16 percent (212).
9% vs 3%	More **Black patients with breast cancer and COVID-19 required mechanical ventilation** than white patients with breast cancer and COVID-19, 9 percent versus 3 percent (213).
34% vs 20%	**COVID-19 patients with active cancer were more likely to die** than those with no history of cancer, 34 percent versus 20 percent (214).
45% vs 12%	**Mortality rate for cancer patients with COVID-19** was 45 percent for those who were **receiving an anti-CD20 anticancer treatment** compared to 12 percent for those who were receiving an anti-Janus Kinase inhibitor anticancer therapy (215).
16% vs 3%	Sixteen percent of **COVID-19 patients with lung cancer who required admission to an intensive care unit** compared to 3 percent of COVID-19 patients without lung cancer (216).

(219)—showed that most patients with solid tumors developed a functional and durable immune response to SARS-CoV-2 infection, lasting at least 11 months. Patients with hematologic malignancies, on the other hand, had impaired immune responses that were related to the type of cancer as well as the treatment patients were receiving (220).

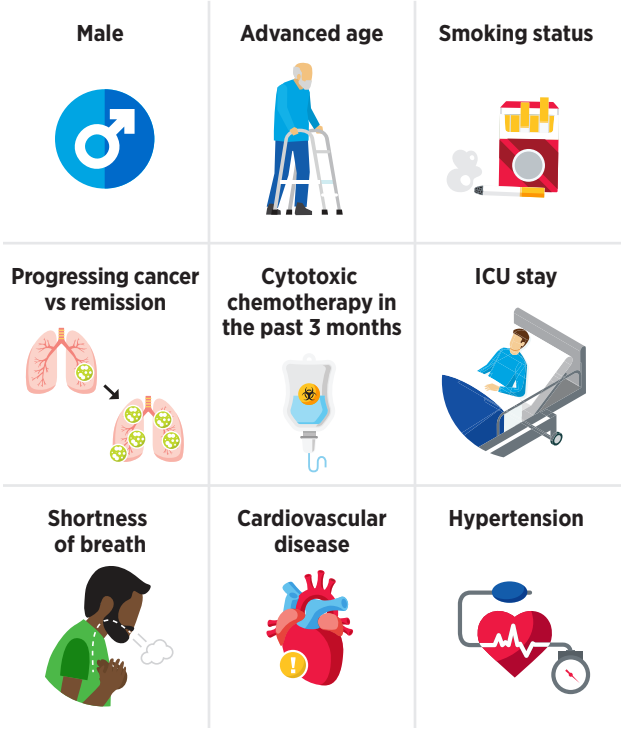
Greater risk of COVID-19 infection and death in patients with cancer has spurred the establishment of multiple collaborative registries across the globe (see **Table 3**, p. 45) to document the interplay between COVID-19 and various aspects of cancer and anticancer treatments. Studies utilizing these resources have provided a deeper understanding of clinical features in patients with cancer that are associated with the risk of adverse COVID-19 outcomes (205,217,222-228,228a). Breast and prostate cancers are the most frequently detected types of cancer among patients with COVID-19 (five to 18 percent, and one to 14 percent, respectively) (229). In the following sections, we focus on the current knowledge of cancer types and anticancer treatments that have the worst impact on the outcome of COVID-19 in patients with cancer.

PATIENTS WITH HEMATOLOGIC CANCERS

Hematologic or blood cancers—leukemias, lymphomas, and multiple myeloma—affect cells that constitute the immune system. Patients with hematologic cancers require frequent hospital visits and/or prolonged stays for treatment, management of complications, and disease monitoring. Because of the nature of hematologic cancers and depending upon the treatment regimen, these patients are generally immunocompromised and thus are at a higher risk of SARS-CoV-2 infection (see sidebar on **Why Are Cancer Patients at an Increased Risk of Infection?**, p. 44).

Overwhelming evidence indicates that patients with hematologic cancers not only experience significantly higher rates of COVID-19 infection and complications, but also exhibit a two- to three-fold higher mortality rate compared to patients without cancer or those with solid tumors (155,210,230-236). Furthermore, a meta-analysis of COVID-19 outcomes in 3,377 patients with hematologic cancers across 38 studies found that the overall

FIGURE 5 DETERMINANTS OF MORTALITY IN PATIENTS WITH CANCER AND COVID-19



Multiple studies have identified key risk factors for mortality in patients with cancer and COVID-19. These include male sex and advanced age of the patient, history of smoking, stage of cancer, recent history of anticancer treatment, pulmonary disorders such as chronic obstructive pulmonary disease and dyspnea (shortness of breath), cardiovascular diseases, and hypertension.

ICU: intensive care unit

mortality from COVID-19 was significantly higher in adults with hematologic cancers (34 percent) compared to children with hematologic cancers (four percent) (237). A study of 250 patients in the American Society of Hematology Research Collaborative (ASH RC) registry (see **Table 3**, p. 45) found an overall mortality rate of 28 percent, with worse outcomes in patients who were diagnosed with hematologic cancer within the past year and whose cancer had relapsed after initial treatment (238). Another meta-analysis that included nearly 5,000 patients with cancer across eight studies found that the risk of COVID-19-related death was 47 percent greater in patients with hematologic cancers compared to those with solid tumors (239). These findings are further substantiated by recent results from a large study encompassing nearly 400,000 adult patients with cancer, 63,413 of whom were also COVID-19 positive, showing that patients with hematologic cancers had a higher mortality rate (17 percent) compared to

Meta-analysis is a process that analyzes data from different studies done about the same subject. The **results of a meta-analysis are usually stronger** than the results of any study by itself (242).

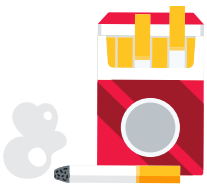
patients with other types of cancer (e.g., the mortality rate in patients with breast cancer was seven percent) (240). Researchers are also learning that patients with certain subtypes of blood cancers, such as acute myeloid leukemia, have a higher mortality rate compared to those with lymphomas (241).

As evident from presented data, the reported mortality rates among COVID-19 patients with hematologic malignancies vary across studies, likely because of the variability in patients' demographic attributes—such as socioeconomic status and age—and clinical characteristics—such as the subtype of hematologic cancer and/or other comorbidities. It is, however, clear that patients with hematologic cancers are at a significantly higher risk of severe COVID-19 and death compared to patients with solid tumors or COVID-19 patients with no history of cancer.

PATIENTS WITH LUNG CANCER

Patients with lung cancer are also uniquely vulnerable to COVID-19 and carry a disproportionately higher burden of severe illness and death from the disease (243-245). Reasons for these unfavorable outcomes are likely multifactorial. Lung cancer patients often have lung damage or lower lung capacity because of the cancer itself or treatments received such as radiotherapy and surgery (see sidebar on **Why Are Cancer Patients at an Increased Risk of Infection?**, p. 44). For example, lung cancer can cause blockage of up to 30 percent of the major airways in patients with advanced-stage lung cancer (246). Another common consequence of advanced-stage lung cancer is the buildup of fluid around lungs, which can restrict breathing (247). Most patients with lung cancer also exhibit multiple risk factors—such as aging, smoking, and pulmonary and cardiovascular issues—that are associated with worse outcomes from COVID-19 (see **Increasing Risk for COVID-19**, p. 22) (216). Moreover, COVID-19 is primarily a respiratory illness that can cause lasting damage to lungs (248), further compounding the adverse outcomes for patients with lung cancer.

Compared to individuals who have never smoked, individuals with a **history of tobacco smoking**, a leading cause of lung cancer, are **more than twice as likely to develop severe COVID-19 and die from it** (249).



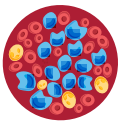
WHY ARE CANCER PATIENTS AT AN INCREASED RISK OF INFECTION?

Risk of a patient with cancer for contracting infections, including infection from SARS-CoV-2, varies depending upon the type of cancer and/or treatment. Additionally, certain medical conditions can increase the risk of infections among patients with cancer.

The type of cancer a patient has—

Blood cancers, such as leukemias, lymphomas, and multiple myeloma

Because these cancers often cause abnormal proliferation and compromised functions of immune cells and a weakened immune system.



Solid tumors, such as lung, breast, or prostate cancer

Because these cancers can enter bone marrow and compete with normal cells for space and nutrients, which can compromise production of new immune cells.

Other ways patients with cancer can become more vulnerable to infections include:

- A **tumor growing on skin** can damage the skin layers and cause pathogens to enter the body.
- A **tumor growing near major blood vessels** can press on them, thus restricting the circulation of oxygen, nutrients, and immune cells to nearby normal tissues, and making them susceptible to pathogens.
- A **tumor growing in lung** can block drainage of mucus, which normally functions as a protective layer of airways, but can provide an environment for growth of pathogens if persistently accumulated.

The type of treatment a patient with cancer is receiving—

Certain drugs that target and deplete or alter the function of normal B cells, which make infection-fighting antibodies

Examples include CAR T-cell therapies; drugs that target specific proteins, such as CD20 and CD38, found on the surface of B cells; inhibitors of proteins important for the B-cell function; and corticosteroids. Based on the current knowledge, this is the most important treatment-related risk factor for severe disease (221).

Certain surgical procedures

Examples include patients with cancer who have their spleens surgically removed, because the spleen plays an important role in detecting and clearing pathogens in blood.

Certain radiation therapies

Because they can result in a decreased number of white blood cells.

Certain chemotherapeutics

Because they can result in a decreased number of immune cells that help fight infections.

Certain molecularly targeted therapies

Because they can weaken the immune system, depending on the protein the drugs are targeting in cancer cells.

Other factors—

Stem cell transplantation

This procedure to replenish the bone marrow stem cells destroyed by the cancer treatment can weaken the immune system.

Poor nutrition

Malnourishment, either because of the type of cancer or anticancer treatment, can weaken a patient's immune system.

TABLE 3 MAJOR COVID-19 AND CANCER REGISTRIES*

Name	Cancer Type	Eligibility Criteria	Region(s) Covered
COVID-19 and Cancer Consortium (CCC19)	Blood cancers and solid tumors	Patients age >18 years with suspected or laboratory-confirmed COVID-19	North America, European Union, United Kingdom, and Argentina
OnCovid	Blood cancers and solid tumors	Patients age ≥18 years with confirmed COVID-19	United Kingdom, Spain, Italy, Germany
UK Coronavirus Cancer Monitoring Project (UK CCMP)	Blood cancers and solid tumors	Confirmed COVID-19	United Kingdom
Thoracic Cancers International COVID-19 Collaboration (TERAVOLT)	Thoracic cancers	Confirmed COVID-19	34 countries from five continents
American Society of Clinical Oncology Survey on COVID-19 in Oncology Registry	Blood cancers and solid tumors	Patients with COVID-19 with active cancer or cancer-free for less than 12 months and receiving adjuvant therapy at the time of COVID-19 diagnosis	United States
American Society of Hematology Research Collaborative (ASH RC)	Blood cancers	Confirmed COVID-19 and hematologic condition (cancer and noncancer)	United States
European Society for Medical Oncology COVID-19 Care (ESMO-CoCARE)	Blood cancers and solid tumors	Confirmed COVID-19	Europe, Africa, and Asia
NCI COVID-19 in Cancer Patients Study (NCCAPS)	Blood cancers and solid tumors	Patients from all age groups who received a positive test result for SARS-CoV-2	United States
Global Registry of COVID-19 in Childhood Cancer	Blood cancers and solid tumors	Patients less than one year old to 18 years old with cancer and COVID-19	51 countries from four continents
The Leukemia and Lymphoma Society National Patient Registry	Blood cancers	Patients with blood cancer with or without COVID-19	United States

*Only selected registries with 1,000 or more patients accrued are included in the table.

An analysis of 21 studies from across the globe, covering more than 2,000 patients with cancer, found that lung cancer was the most frequently detected type of cancer among patients with COVID-19 (250). With a few exceptions (245,251,252), studies have found that patients with lung cancer are at a significantly higher risk of death from COVID-19 compared to patients with other cancer types (235,244,253,254). One review, examining data from eight independent studies covering patients with cancer and COVID-19, including more than 700 patients who had lung cancer, found that the mortality rate in patients with lung cancer was higher compared to the rate in patients who had other types of cancer and ranged from 14 percent to 55 percent (255). Another analysis of 13 studies from multiple countries investigating a link between COVID-19 and lung cancer found that the mortality rate in patients with lung cancer with COVID-19 was 42 percent, which is significantly higher than 24 percent in patients with other cancer types. Interestingly, this difference in mortality rate was not significant when studies from China were also included in the analysis (256), indicating that the geographic location, ethnicity, and/or genetic makeup of the patient population may also determine mortality rates among patients with cancer and COVID-19. Such analyses also point to the need of region-specific large studies to determine the optimal course of COVID-19 management that is tailored to the specific needs and unique characteristics of patients with cancer.

PEDIATRIC PATIENTS WITH CANCER

As of December 30, 2021, almost 7.9 million of all COVID-19 cases in the U.S. were children, according to a joint report from the American Academy of Pediatrics and the Children's Hospital Association (257). Like adults with cancer, children with cancer are frequently immunocompromised, raising concerns at the onset of

Continued on page 47

JULIE CAMPBELL
Age: 64 | Vineland, NJ

Fighting COVID-19 While Undergoing Treatment for Breast Cancer

In October of 2020, Julie Campbell, a real estate professional from New Jersey and a patient with chronic myelogenous leukemia (CML), was just getting her life back to normal. Her recent tests found no leukemia in her blood and, since she had been in remission for a while, her physician discontinued her chemotherapy.

Unfortunately, exactly one month after she was taken off her chemotherapy for leukemia, she was diagnosed with stage IV triple-negative breast cancer. While she had an extremely difficult time dealing with her initial diagnosis of leukemia, Julie felt that she was better prepared when she learned about her breast cancer.

"Leukemia was a nightmare, and it took me years to be okay with that. And so, when I got the breast cancer, believe it or not, it was not as bad," she said. "I think the CML diagnosis prepared me for the second cancer. I was concerned, obviously, but more concerned with how my family would feel and how afraid they would be."

Because Julie was diagnosed during the pandemic, her oncologist, Ana Maria Lopez, MD, MPH, of Jefferson Health, and her health care team had to work together using telemedicine to communicate effectively and come up with treatment plans. Julie started receiving chemotherapy, which was followed by radiotherapy. However, battling cancer in the middle of a global pandemic turned out to be a serious challenge.

Julie knew that her immune system was compromised, not only because of leukemia and its treatments but also due to the more recent chemotherapy she was receiving for her breast cancer. To protect herself from contracting COVID-19, she stayed vigilant of her health and practiced every precautionary measure.

"I was being extremely safe. I didn't go shopping; I didn't go to the restaurants; I stayed home," Julie said. "My husband did all the shopping and we wore masks in the house. My son had to stay away from me when he was in school. We kept him home from school for a while so he wouldn't bring anything back."

Receiving treatments also became more stressful because every time she went to the clinic she was worried about contracting COVID-19. As soon as the COVID-19 vaccines became available, Julie received the recommended regimen. She wanted to make sure that she had done everything she was able to do to protect herself. Unfortunately, Julie and her son, husband, and sister all contracted COVID-19.

Julie was in the midst of receiving radiotherapy for her breast cancer when she tested positive for COVID-19. She had to delay her treatment. At the request of her daughter, who is a respiratory therapist, Julie took herself to a hospital.

"My oxygen level was very low, and they admitted me. And all I can remember is the fear on my daughter's face, as she said 'Mom, you can't go on a ventilator. You have to breathe,'" Julie remembered.

Julie followed every instruction given to her by the health care team including her pulmonologist. At the end of eleven days, she was able to leave the hospital. Other than some residual lung issues, she was in great shape. However, she is still practicing great caution. Even though she is fully vaccinated and has received additional vaccine doses, her physician worries about the level of protection she has.

"My pulmonologist thinks that the booster is what saved my life. However, he wasn't sure that my body had built up enough antibodies," she said. "He told me to be extremely cautious and I was back to living my life in a bubble."

Delaying treatment was stressful for Julie. She worried that her disease might spread, given the aggressive nature of triple-negative breast cancer. After recovering from COVID-19, she was able to resume her radiation therapy. However, after the last three treatments, her physician recommended that she discontinue. The area that they were treating had shown new signs of cancer and it did not make sense to continue with the radiation.

Dr. Lopez has recommended diagnostic testing to evaluate Julie's cancer and identify the best future course of treatment. However, Julie's experience from the past year has left her concerned.

"I still am kind of nervous going into doctors' offices. I'm worried about contracting COVID again," she said. "I just want to get into a normal life, where I don't have to worry about COVID, but that's not going to happen as long as the pandemic continues, and people refuse to get vaccinated. They don't see that it's not just about them; it's also about patients like me and our families."

the pandemic that COVID-19 will have disproportionately adverse effects on children (258). Initial evidence in early 2020 suggested that immunocompromised children and adolescents do not have increased incidence of, or severe outcomes from, COVID-19 as opposed to adults with compromised immune systems. Fortunately, current data suggest that asymptomatic disease or mild effects on the respiratory system, such as cough and sore throat, are the most common COVID-19-related symptoms in children with cancer (259). The reasons for mild impact of COVID-19 on children with cancer are currently unknown. Although significantly lower compared to adults, pediatric cases still exhibit severe disease compared to general population (260-262).

An analysis of 16 independent studies from around the globe investigating the impact of COVID-19 on children and adolescents with cancer found that pediatric patients with cancer were at a decreased risk of death compared to adult patients with cancer, but were at a greater risk of death when compared to the general pediatric population (258). Findings also indicated that the clinical outcomes in children with cancer may be worse if they belong to certain high-risk demographics, such as male or obese individuals, or have hematologic cancers (see **Patients with Hematologic Cancers**, p. 42). A recent study of 1,500 children and adolescents with cancer and COVID-19 from 131 institutions in 45 countries indicated that 20 percent of the pediatric patients had a severe COVID-19 infection, and about four percent of all patients died, a death rate that is more than four times higher than that of the general pediatric population with COVID-19 (263). Children with cancer have additionally suffered from the adverse effects of the pandemic across the cancer care continuum. Studies are underway to establish the long-term impact of COVID-19 on both physical and mental health in children with cancer in the U.S. (264) and worldwide (265).

PATIENTS WITH CANCER ON ACTIVE ANTICANCER TREATMENT

Certain types of cancer treatments, such as chemotherapy, can reduce the number of immune cells in the body, weakening the immune system and increasing the vulnerability of patients with cancer to infections (see sidebar on **Why Are Cancer Patients at an Increased Risk of Infection?**, p. 44). A better understanding of the correlation between active anticancer treatment and higher mortality rates in patients with COVID-19 and cancer is emerging. A study of more than half a million COVID-19 patients, which included more than 14,000 patients who also had cancer, found that the mortality rate was highest in patients with cancer who had received an anticancer treatment within three months before COVID-19 diagnosis (7.8 percent) compared to patients with no recent cancer treatment (5.0 percent) and patients without cancer (1.6 percent) (266). Another study found that, compared to other types of anticancer treatments, such as molecularly targeted therapy, patients with cancer who received surgical treatment within 40 days of contracting COVID-19 demonstrated higher rates of death (25 percent) and higher chances of ICU admission (37.5 percent), and were likely to develop severe or critical symptoms (62.5 percent) and require invasive ventilation (25 percent) (235).

A meta-analysis from 29 studies, including more than 5,000 patients with cancer and COVID-19, found that even though chemotherapy more than doubled mortality in patients with hematologic cancers, there was no correlation between solid tumors and increased chances of death due to anticancer treatment (267). Similarly, an analysis of available data on the use of immune checkpoint inhibitors suggested that use of these anticancer therapeutics did not increase COVID-19-related mortality (268). However, another analysis of 16 studies, covering more than 3,000 patients with cancer and COVID-19, found that severity of COVID-19, as well as mortality, was higher with anticancer treatment compared to no treatment (267). These seemingly conflicting reports point to the heterogeneity of cancer and anticancer therapies, as well as the diversity of the patient population, and indicate that additional research is needed to firmly establish the effect of anticancer treatments on COVID-19-related outcomes (269).

PREVENTION AND TREATMENT OF COVID-19 IN PATIENTS WITH CANCER

Patients with cancer constitute one of the groups most vulnerable to severe complications and death from COVID-19 (see **Burden of COVID-19 in Patients with Cancer**, p. 41) and should take extra care to protect themselves from COVID-19. With a wider availability of highly effective vaccines against COVID-19 (see sidebar on **SARS-CoV-2 Vaccination Recommendations**, p. 28), getting vaccinated is the first line of defense against SARS-CoV-2 infection (see sidebar on **COVID-19 Vaccines and Patients with Cancer**, p. 48). Findings from a large study showed that patients with cancer had a 58 percent less chance of SARS-CoV-2 infection after receiving the second dose of one of the mRNA vaccines against COVID-19 (270). In addition, experts from CDC and multiple other health care organizations recommend that patients with cancer continue to exercise all preventive measures, including getting tested, wearing a mask, social distancing, frequently washing hands, avoiding crowded gatherings, and minimizing nonessential travel.

Each patient with cancer has a unique risk for COVID-19 because of the type of cancer, anticancer treatment, and any other medical conditions (see **Burden of COVID-19 in Patients with Cancer**, p. 41). Available evidence (see **Varied Responses to COVID-19 Vaccines in Patients with Cancer**, p. 47) suggests that patients with certain types of cancer (such as those with hematologic cancers), or those receiving certain types of anticancer treatments, should exercise additional care and identify the best time to get vaccinated during their experience with cancer in consultation with their health care provider teams.

VARIED RESPONSES TO COVID-19 VACCINES IN PATIENTS WITH CANCER

There is strong evidence that patients with cancer are vulnerable to COVID-19 infection and, when infected, do not mount a strong immune response (see **Burden of COVID-19 in Patients with Cancer**, p. 41), prompting AACR and several other cancer-focused professional organizations to recommend that patients with cancer be prioritized to receive vaccination against COVID-19 (204,280,281) and that additional doses of vaccines be given to patients with cancer who have already received

COVID-19 VACCINES AND PATIENTS WITH CANCER

The current guidance from the Centers for Disease Control and Prevention (CDC) for patients with cancer is to receive recommended dose(s) of one of the three approved COVID-19 vaccines to prevent SARS-CoV-2 infection and/or severe disease. Because of the complex nature of cancer, and how anticancer treatments affect the immune system, responsiveness of patients with cancer to COVID-19 vaccines is an area of active research, rapidly yielding new information. It is important for patients with cancer to discuss risks and benefits of receiving one of the COVID-19 vaccines with their health care providers, who can offer up-to-date information and expert advice for the best time to receive a COVID-19 vaccine.

Here we summarize the state of the current knowledge on COVID-19 vaccination for patients with cancer and their caregivers:

Should patients with cancer, including those receiving active anticancer treatment, get vaccinated?	Yes. CDC and multiple expert panels recommend that all patients with cancer, including those who are being actively treated for their cancer, should receive one of the three COVID-19 vaccines that have been approved by the Food and Drug Administration for the general population (271). Patients with cancer should get vaccinated as soon as possible. Furthermore, their response to primary vaccination may wane over time, so they should keep in close consultation with their health care provider teams to determine if and when they will need additional vaccination (272,273).
Are vaccines safe for patients with cancer and survivors of cancer?	COVID-19 vaccines are safe for patients with cancer (274) and cancer survivors.
Are vaccines effective in patients with cancer?	Vaccines are effective in patients with cancer. However, emerging data suggest that the response to COVID-19 vaccines in patients with cancer varies depending on the type of cancer as well as the anticancer treatment (152,275-277).
What else can one do to minimize the risk of SARS-CoV-2 infection and/or severe COVID-19 for patients with cancer?	Any caregiver or person in close contact with a patient with cancer, including those living in the same household as the patient with cancer, should also get vaccinated.
Should a patient with cancer who has been fully vaccinated continue to follow CDC recommendations to prevent the spread of COVID-19?	Yes. Because certain patients with cancer may not elicit the expected strong immune response to vaccination, a fully vaccinated patient with cancer should continue to follow CDC recommendations to prevent the spread of COVID-19, including wearing a mask, maintaining social distance, frequently washing hands, avoiding crowded gatherings, minimizing nonessential travel, and any other protective measures.
Does vaccination impact screening for certain cancers?	Possibly. Studies have found that, like other vaccines, COVID-19 vaccines can cause swollen lymph nodes (278). Swollen lymph nodes can affect interpretation of imaging results, especially in mammograms that are used to screen for breast cancer. Experts recommend delaying imaging by four to six weeks after getting vaccinated, and patients with breast cancer should discuss with their health care providers the optimal time to schedule a mammogram in relation to vaccination against COVID-19.
Should a patient with cancer get additional primary and/or booster dose(s) of COVID-19 vaccine?	Yes. CDC recommends additional primary and/or booster dose(s) of either the Pfizer/BioNTech or Moderna vaccine for people who are immunocompromised, including those receiving active cancer treatment for solid tumors or hematologic cancers (279).

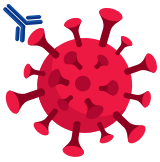
HOW IS THE IMMUNE RESPONSE TO COVID-19 VACCINES EVALUATED?

There are two ways that researchers are able to determine the strength of the immune response to COVID-19 vaccines:

By Measuring Antibodies

Following either SARS-CoV-2 infection or COVID-19 vaccination, an effective immune response relies on specialized immune cells, called B cells, to produce two types of antibodies that typically become detectable in the blood one to three weeks after the infection:

Binding Antibodies



How do they work?

By attaching to SARS-CoV-2, these antibodies mark it for destruction by immune cells.

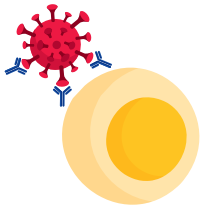
How are they detected?

Binding antibodies can be detected using fluorescence signals detected from a specialized technique called enzyme-linked immunosorbent assay (ELISA).

How do they determine the immune response to vaccination?

Robust signal reflects higher quantities of SARS-CoV-2-specific antibodies in the sample and stronger immune response to vaccination.

Neutralizing Antibodies



How do they work?

These antibodies directly inhibit the ability of a pathogen, such as SARS-CoV-2, to infect cells in the body.

How are they screened?

Neutralizing antibodies can be screened by imaging techniques known as plaque reduction neutralization test (PRNT) or microneutralization assay.

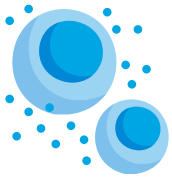
How do they determine the immune response to vaccination?

Both assays measure quantities of neutralizing antibodies in the blood; PRNT uses nonfluorescence approach and microneutralization assay uses fluorescence dyes. Higher quantity of neutralizing antibodies means stronger response.

By Measuring T Cells

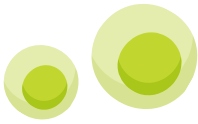
Following exposure to COVID-19, the body may produce different types of T cells, the immune cells that help protect the body from infections:

Helper T Cells



Helper T cells produce molecules, called cytokines, that function as chemical signals to stimulate the immune response by activating other immune cells, including the antibody producing B cells and the cytotoxic T cells.

Cytotoxic T Cells



These specialized immune cells eliminate cells that are infected with the virus.

How are they screened?

The number of T cells can be measured by the enzyme-linked immunospot (ELISPOT) assay.

How do they determine immune response to vaccination?

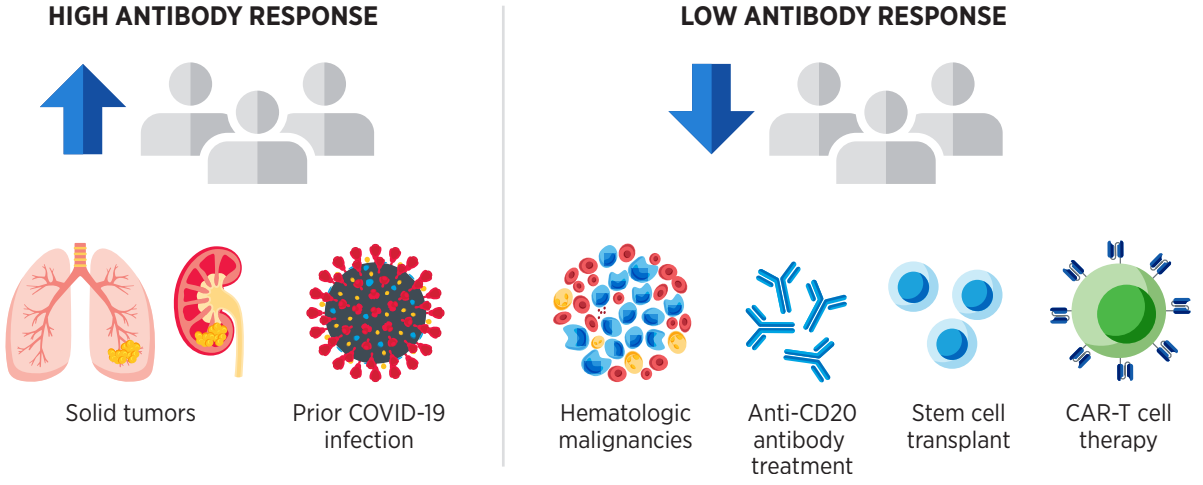
Change in color of cytokine-specific dyes indicates the presence of SARS-CoV-2-specific T cells in the sample, and the intensity of the change reflects the strength of the immune response.

Modified from (287).

their primary vaccination regimen (see sidebar on **SARS-CoV-2 Vaccination Recommendations**, p. 27) (204,280-282). Furthermore, experts recommend that patients with cancer be included in ongoing as well as future clinical trials of the vaccines, because these patients are vulnerable to COVID-19, yet were largely excluded from the initial clinical trials testing COVID-19 vaccines (283,284).

Currently available evidence suggests that the response to COVID-19 vaccines in most patients with cancer is

FIGURE 6 RESPONSE TO COVID-19 VACCINES VARIES IN PATIENTS WITH CANCER

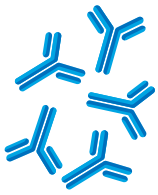


Since the availability of COVID-19 vaccines, several studies have quantified the production of anti-SARS-CoV-2 antibodies as well as levels of immune cells in response to COVID-19 vaccines in patients with cancer. Findings of these studies suggest that most patients with solid tumors produce antibodies and mount cellular responses, depicted as an upward blue arrow in the left panel, that are similar to those without history of cancer. However, there is a subset of patients with cancer who do not respond, or the strength of their response is weaker compared to that of healthy individuals (shown as a downward blue arrow in right panel). These patients include those who have hematologic malignancies, have received anticancer therapy that targets and depletes antibody-producing B cells (e.g., anti-CD20 antibody treatment or CAR T-cell therapy), or have received stem cell transplant.

comparable to that of the general population, with some notable exceptions (see **Figure 6**, p. 50) (150,285,286). Researchers are actively working to fully understand the response to COVID-19 vaccines in patients with cancer (see sidebar on **How Is the Immune Response to COVID-19 Vaccines Evaluated?**, p. 49), and are also exploring ways to improve the responsiveness to COVID-19 vaccines in patients with cancer. An active area of research is to combine hyperimmune intravenous immunoglobulin (IVIG), which contains antibodies taken from people who have previously had COVID-19 (see sidebar on **What Types of Treatment Are Being Investigated for COVID-19?**, p. 33), with COVID-19 vaccines to invoke a strong immune response in patients with compromised immune system.

Vaccine Response in Patients with Hematologic Cancers and Solid Tumors

In addition to the evidence that patients with hematologic malignancies are at a higher risk of severe infection and death from COVID-19 (see **Patients with Hematologic Cancers**, p. 42), there is also evidence that they have a less robust immune response to COVID-19 vaccines (150,276,288-295). This is because not only do hematologic malignancies compromise the immune system of patients, but also certain treatments—such as chemotherapy, stem cell transplantation, and adoptive cell therapies—can further damage the immune system.



- Patients with **detectable antibodies against a pathogen in the blood** are considered **seropositive**, for example, a healthy individual who has been infected with the SARS-CoV-2 virus.
- Individuals with **no detectable antibodies against the virus in the blood** are considered **seronegative**, for example, healthy individuals who have not been exposed to SARS-CoV-2, or patients with blood cancer who have been exposed to SAS-CoV-2 or received the COVID-19 vaccine but recently received or are actively receiving anticancer treatments that deplete B cells or modify their function, such as **Larry Saltzman, MD** (see p. 52).
- The **percentage of individuals in a population who have antibodies against the virus** is called **seroprevalence** and indicates how many individuals have been previously infected with SARS-CoV-2.

According to one study, **79 percent** of **patients with solid tumors** had **antibodies against SARS-CoV-2 six months after receiving the second dose of the BNT162b2 vaccine** compared to 84 percent of healthy individuals (296).

Patients who have hematologic cancers affecting B cells, which produce antibodies that are important for fighting off pathogens (e.g., SARS-CoV-2), are particularly vulnerable. In one study examining the immune response to the mRNA-1273 and BNT162b2 vaccines in patients with hematologic malignancies, almost all patients with non-Hodgkin lymphoma (NHL), the most common B-cell malignancy, were seronegative; the percent of seronegative NHL patients depended on the subtype of NHL and ranged from 21 percent in patients with diffuse large B-cell lymphoma to 56 percent in patients with mantle cell lymphoma (290). Similarly, variable rates of response to COVID-19 vaccines have been observed in patients with multiple myeloma, another type of blood cancer that affects B cells (297). Furthermore, a recent study found that patients with multiple myeloma who have completed the primary vaccination course still exhibit a significantly higher rate of breakthrough infections than the general population (298). Patients with leukemia and myelodysplastic syndromes, on the other hand, appear to exhibit vaccine responses that are comparable to that of healthy individuals (291,299-307).

Mortality rate among COVID-19 patients with lung cancer is significantly higher compared to the general population (235,308). Encouragingly, a recent study shows that COVID-19 vaccines are safe and effective in patients with thoracic cancer, including lung cancer; most patients had adequate antibody levels against SARS-CoV-2 after two doses and vaccines were safe in 90 percent of the patients (309).

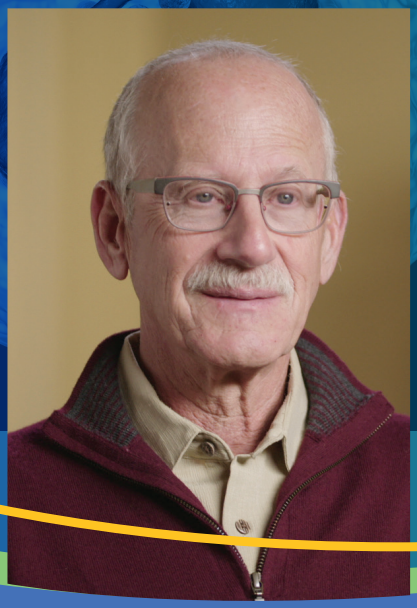
Vaccine Response in Patients with Cancer on Active Anticancer Treatment

Evidence is accruing that the anticancer treatments which modify or deplete B cells are a significant factor in a decreased immune response (291,299-302). One example is the anticancer treatments—for example, rituximab or obinutuzumab—targeting the CD20 protein, which is abundantly present on the surface of B cells important for mounting an effective immune response against pathogens (e.g., SARS-CoV-2). In a recent study, 80 percent of the patients with NHL who received either rituximab or obinutuzumab more than a year ago had a seropositive response to the BNT162b2 vaccine compared to just three percent of the patients who had received their last anti-CD20 treatment within 45 days of getting vaccinated (303). Importantly, a third dose of either of the mRNA vaccines increased antibody levels in more than 50 percent of the patients with B-cell malignancies who had not responded to the first two doses of the vaccines (304). However, patients with cancer who were on active or recent anticancer treatment or those receiving CAR T-cell therapies that specifically targeted proteins present on B cells, such as **Larry Saltzman, MD** (see p. 52), exhibited a poor response even to the third dose (305-307). Among these patients, those who received IVIG (see sidebar on **What Types of Treatment Are Being Investigated for COVID-19?**, p. 33) as part of their blood cancer treatment had high levels of antibodies against the spike protein of SARS-CoV-2 virus, according to recent findings (310). Equally interesting are the reports that the levels of anti-spike antibodies in IVIG, which is derived from blood plasma donors, have increased dramatically as more members of the U.S. population have either had COVID-19 or have been vaccinated (311). Studies with large number of patients are needed to determine whether administration of IVIG with high levels of anti-spike antibodies can benefit a broader population of immunocompromised patients who do not produce antibodies against the virus even after the additional vaccine doses.

Apart from anticancer treatments that affect B-cell functions, other types of anticancer treatment appear to have minimal impact responsiveness to COVID-19 vaccines. For example, one study reported no adverse effects of COVID-19 vaccines in patients whose cancer was being actively treated with immune checkpoint inhibitors (312). Another study investigating effects of COVID-19 vaccination in patients with cancer who were being treated with immune checkpoint inhibitors found no new immune-related side effects or exacerbation of existing immune-related side effects after administration of the BNT162b2 mRNA vaccine (313). Another study further corroborated that there were minimal or no side effects of COVID-19 vaccination in patients with cancer undergoing active treatment compared to healthy individuals (314).

Because of the complex nature of cancer and its treatments, several professional organizations focused on clinical cancer care have issued guidance for patients with cancer receiving various types of treatment regarding the need to get vaccinated against COVID-19 (272,281,315). Additionally, patients with cancer should consult their health care teams about the timing and benefits of COVID-19 vaccination. One ongoing clinical study—the Vaccination Against COVID-19 in Cancer or VOICE (316)—is specifically investigating the effects of various anticancer treatments on the response to COVID-19 vaccines (see sidebar on **COVID-19 Vaccines and Patients with Cancer**, p. 48). Recent findings from the study show that, compared to 99.6 percent of the control group, 93.1 percent of patients with solid tumors who were being treated with immunotherapy, 83.8 percent of those on chemotherapy, and 88.8 percent of the patients receiving both types of treatment achieved an adequate response to the mRNA-1273 vaccine 28 days after receiving the second dose of the vaccine. Of note, adequate response was defined as antibodies produced against the spike protein of SARS-CoV-2 virus by the body in response to vaccination at levels sufficient to neutralize the virus. Another study showed that, while 90 percent of patients with cancer produced antibodies in response to COVID-19 vaccination, the antibody levels were four times lower in cancer patients who were receiving a combination of chemotherapy and immunotherapy, indicating that a comprehensive examination of the impact of various combinations of anticancer therapies on the responsiveness to COVID-19 vaccines is needed (317). Future studies will continue to refine our knowledge of the effects of COVID-19 vaccines and specific cancer treatments on clinical outcomes for patients with cancer.

Continued on page 53



LARRY SALTZMAN, MD
Age: 68 | Sacramento, CA

Participating in a Clinical Trial for CAR T-cell Therapy During a Global Pandemic

Since his diagnosis with chronic lymphocytic leukemia in January 2010, life for Larry Saltzman, a board-certified family physician, has been a roller coaster. In the past 11 years, he has gone through several therapies, three clinical trials, several recurrences, and some serious side effects from his treatments.

One of the challenges that he faces is being immunocompromised during the COVID-19 pandemic as a result of leukemia treatments that depleted his body of B cells that make antibodies. This makes him more vulnerable to infections including COVID-19 because he does not have the protection usually conferred by vaccination.

"I know through some blood testing that the COVID-19 vaccines have not produced any antibody response in my system," Larry said. "When I was in chemotherapy, I was very careful about being in public. I learned how to not shake hands and how to elbow bump with people. And with the world we're living in today, I'm even more secluded because I have no immunity. So, I'm very careful."

As a result, Larry is an avid advocate of vaccination.

"I rely on people around me to get vaccinated and protect themselves," he said. "Ultimately that protects me from this infection. And it is just very hard to stomach when I hear about people who are vaccine hesitant."

In December of 2009, Larry felt some bumps on his neck that turned out to be swollen lymph nodes. Follow-up tests led to a diagnosis of leukemia. Upon his physician's recommendation, Larry followed a "watch and wait" approach up until 2013, when he had a flare-up and began treatment with a chemotherapeutic.

Since then, he has been on several treatment regimens, including molecularly targeted therapeutics such as ibrutinib (Imbruvica) and, as of December 2019, an experimental immunotherapeutic, known as CAR T-cell therapy, through a clinical trial at the Fred Hutchinson Cancer Research Center in Seattle. The CAR T-cell therapy effectively controlled his cancer but also caused many serious side effects. He was hospitalized twice within a month of receiving the treatment with episodes of cytokine release syndrome.

"The CAR T cells create inflammation… and because it inflames everything, my heartbeats were not normal rhythm. It also affected my lungs and my brain," Larry said.

Following his CAR T-cell treatment at the end of January 2020, Larry returned home to Sacramento. Soon after, the United States was hit by the first surge of the COVID-19 pandemic. Because he was immunocompromised, Larry's health care team urged him to stay at home and avoid any potential exposure to SARS-CoV-2. This caused serious disruption to his participation in the clinical trial, which required regular follow-up care and visits to Seattle. When the country and most of the health care facilities shut down in March 2020, Larry couldn't return to Seattle for the bone marrow biopsies, scans, and blood tests that were part of the clinical trial protocol.

"I was in Sacramento with CAR T-cell treatment that couldn't be stopped. And when I asked my doctors in Seattle, they said: We don't want you on an airplane. We don't want you in Seattle. You'll just have to do the best you can."

The pandemic also took a toll on his social and personal life. Larry and his wife have been reluctant even to go into a grocery store or to travel to Seattle to see their son and his family.

"It's been a real emotional challenge because we are social beings and we have not been able to be social," he said.

Moreover, as a physician, Larry is concerned about the long impact of the pandemic on public health.

"I worry about how many people are missing their mammograms or their colonoscopies, or other preventative treatments or procedures that should be done to keep people healthy."

Another area of patient care that has been adversely impacted by COVID-19 is clinical trials, which are key to the development of new and improved anticancer agents. Although the pandemic has caused a decline in enrollment in clinical trials because patients are worried about exposure to COVID-19, adult recruitment in cancer clinical trials was an ongoing challenge even before the pandemic. There are many barriers, including out-of-pocket costs related to treatments or travel, that deter patients with cancer from enrolling into lifesaving clinical research. This is a real issue that needs to be addressed urgently.

"I think if policy makers could take a closer look at what it takes to manage the preparation and testing of new treatments and what the real cost is, we would all be much better off," Larry said.

COVID-19 VACCINE MISINFORMATION AND HOW TO ADDRESS IT

Researchers working on addressing a scientific hypothesis or theory continually refine, refute, or redefine scientific questions related to their work as new evidence comes to light. Misinformation arises as we seek to better understand and fill in the information gaps that exist because of the lack of scientific evidence. It is important to distinguish misinformation from disinformation, the latter of which is false information deliberately created and disseminated with malicious intent.

Patients with medical conditions, including cancer, frequently seek information and support related to their disease on easily accessible digital publishing platforms, including social media (318-321). Unfortunately, there is also a large body of misinformation and disinformation surrounding the COVID-19 pandemic on these platforms (322), causing a lack of confidence in the available scientific evidence among some patients and their caregivers. The extent of COVID-19 misinformation prompted the U.S. Surgeon General to declare health misinformation an urgent threat to public health in an advisory issued in July 2021 (323).

COVID-19 Misinformation Among Patients with Cancer

Misinformation about COVID-19 vaccines has affected patients with cancer and their caregivers in several ways, as listed below:

- **Parents of children with cancer** were more likely to endorse misinformation about COVID-19, as well as more likely to believe myths associated with COVID-19 prevention, compared to parents of children without any history of cancer (324).
- **Cancer survivors, especially those on active anticancer treatment**, were more vulnerable to COVID-19-related misinformation, while adults without a history of cancer or cancer survivors no longer in treatment were less vulnerable (325).
- **Black patients with COVID-19** are three times as likely to be hospitalized and twice as likely to die as individuals who are white (326), yet only 50 percent of Black individuals have received at least one dose of COVID-19 vaccine (compared to 58 percent of individuals who are white) (327). One possible reason for low vaccination rates in this population is the disinformation among the Black community that high levels of melanin in their skin protect them from SARS-CoV-2 infection (328).
- More than seven percent of 208 **surveyed patients with cancer** indicated intention to delay or abstain from vaccination because of fear of adverse reactions (57 percent of the unvaccinated respondents), fear that vaccine development was rushed (43 percent of the unvaccinated respondents), and insufficient knowledge (64 percent of the unvaccinated respondents) (329).

How to Address COVID-19 Vaccine Misinformation*

Examples above highlight the need to develop effective strategies for addressing COVID-19 vaccine misinformation, which can be life-threatening for vulnerable individuals, such as patients with cancer. Some of the approaches to minimize the spread of misinformation and disinformation in the community include:

- **Lead with the fact and make it clear, relevant, and memorable.**

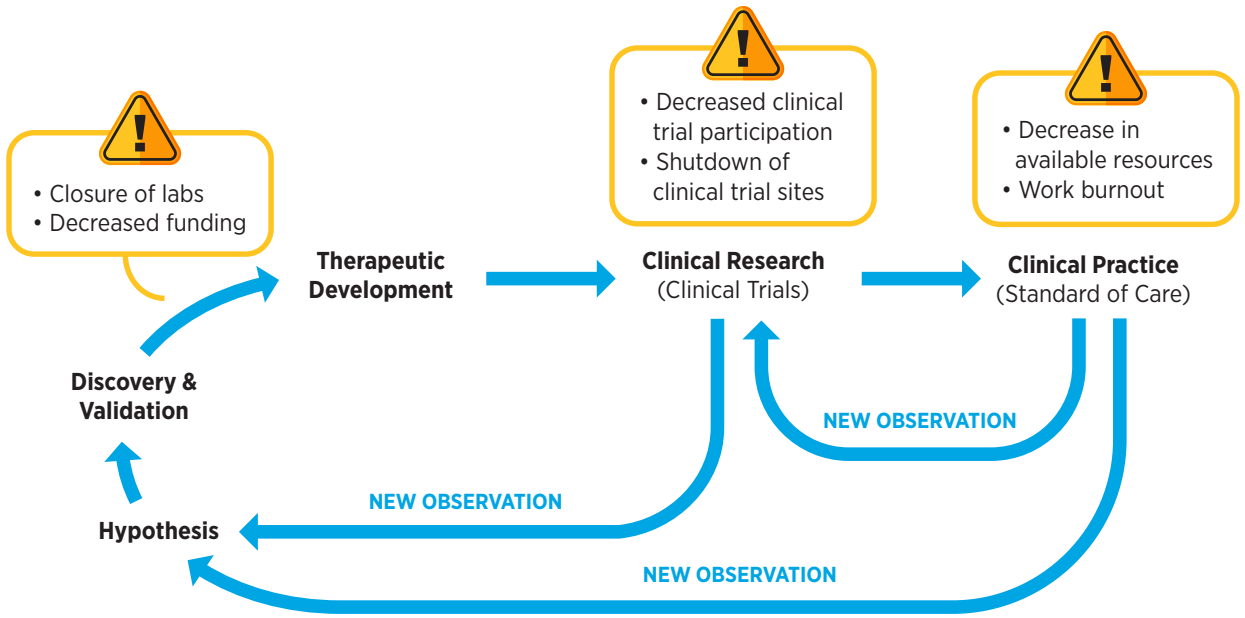
Example: *The COVID-19 vaccine will not make you sick with COVID-19.*

- **If someone is sharing misinformation unintentionally, explain reasons why facts could have been misinterpreted.**
- **If someone is spreading disinformation, identify and highlight misleading tactics and motives and provide alternative, evidence-based information in an easy-to-understand and memorable manner.**

Example: *COVID-19 vaccines teach your immune system to recognize and fight the virus that causes COVID-19 and cannot make you sick with COVID-19. Sometimes this process can cause symptoms, such as fever; these symptoms are normal and are signs that the body is building protection against the virus that causes COVID-19.*

*Developed from (330)

FIGURE 7 DISRUPTION OF THE MEDICAL RESEARCH CYCLE DURING THE COVID-19 PANDEMIC



The medical research cycle is an iterative and self-driven process with a primary goal to save and improve lives. Findings from any type of research can lead to new questions and generate new hypotheses relevant to the practice of medicine. The discovery phase of the medical research cycle uncovers new targets for developing better and more effective treatments. Potential therapeutics first undergo preclinical testing to identify any harmful effects and determine initial dosing. Both the discovery phase and preclinical testing of potential therapeutics were severely impacted by the pandemic because of the nationwide closure of academic institutions, substantial decrease in research funding from philanthropic organizations, and exit of many early-stage investigators from the field, including women and those from ethnic and racial minorities (338-340). Clinical trials that test the safety and efficacy of potential therapeutics were also negatively affected.

Modified from (38).

The overwhelming evidence presented in this section strongly advocates that patients with cancer should be offered, and encouraged to practice, additional means of protection against COVID-19 that include social distancing measures and additional doses of COVID-19 vaccines as have been approved by FDA and endorsed by CDC (279,291,331). It is also imperative to dispel the misinformation surrounding COVID-19 and vaccines against SARS-CoV-2 and provide patients with easily accessible and evidence-based information about the risks of COVID-19 exposure and the lifesaving benefits of vaccination against SARS-CoV-2 (see sidebar on **COVID-19 Vaccine Misinformation and How to Address It**, p. 53).

IMPACT OF COVID-19 ON CANCER SCIENCE AND MEDICINE

The COVID-19 pandemic has adversely affected cancer science and medicine by disrupting multiple aspects of the medical research cycle (see **Figure 7**, p. 54). The pandemic has upended the personal and professional lives of cancer researchers in the U.S. and around the world. These adverse effects include decreased productivity and lost career opportunities among cancer researchers, in particular, among early-stage, minority, and female investigators, because of the closures of and restricted access to research institutions and considerably reduced research funding by philanthropic organizations, which typically contribute up to 50 percent of all cancer research funding in the United States (332) (see **Impact of the Pandemic on Cancer Researchers: A Survey of the AACR Research Grant Awardees**, p. 55); refocused expertise and resources by some cancer researchers to study SARS-CoV-2 (333); substantially reallocated financial resources by many health care systems away from cancer care to address the challenges imposed by the COVID-19 pandemic (334,335); and a significant decline in clinical trial enrollment and conduct (333,336,337). It is important to note that the collective impact of these interruptions on cancer science and medicine is not yet clear, but will likely be far-reaching.

Continued on page 56

IMPACT OF THE PANDEMIC ON CANCER RESEARCHERS

A SURVEY OF AACR RESEARCH GRANT AWARDEES

Methodology*

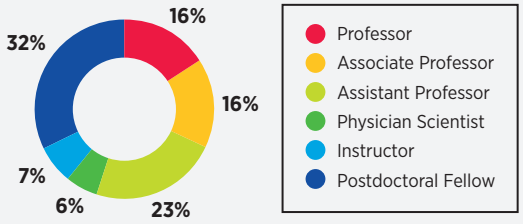
Data collection period: January 4, 2022, to January 12, 2022

Population: The online survey was emailed to 247 cancer researchers in North America, Europe, and Asia who received one of the many research awards that are offered by AACR in the past five years.

Response rate: 40 percent of the survey recipients responded (n=100). Of the 100 respondents, responses from 66 respondents who completed the survey are presented.

Respondents' Demographics

Response to demographics-related questions (race, ethnicity, and sex) was voluntary. Among the respondents who chose to share this information, 57 percent were male, and 43 percent were female. In addition, 51 percent were white; 36 percent were Asian; 12 percent were Hispanic or Latino/a; and one percent were of mixed race. Respondents from all levels of career participated in the survey:

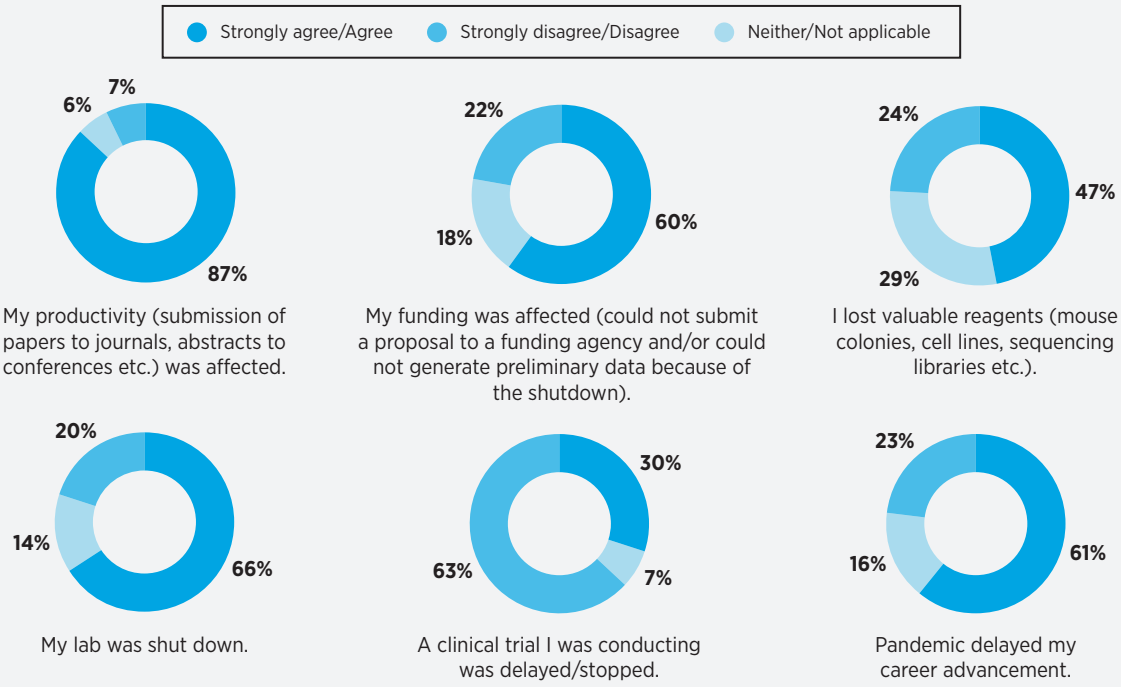


COVID-19 Impact

Has the pandemic affected your research, career in cancer research, and/or patient care?

99% of the respondents said that COVID-19 had negatively impacted their research, career in cancer research, and/or patient care.

How has the pandemic affected your research, career in cancer research, and/or patient care?



*Survey analysis: To identify the impact of COVID-19 on research, and career in cancer research and/or patient care, respondents were presented with a 5-point Likert scale (Strongly Agree, Agree, Neither Agree nor Disagree, Disagree, Strongly Disagree) and not applicable (NA) options. For data presentation, the following sets of responses were combined and presented in this survey as percent of respondents (n=66): Strongly Agree and Agree; Strongly Disagree and Disagree; and Neither Agree nor Disagree and NA.

> **"I started my lab in August 2019 and when the pandemic hit, I was in the set-up phase and just started recruiting personnel to my lab. The pandemic delayed the hiring of lab personnel, reduced the opportunities for funding, and drastically limited the experimental work that I was planning to perform to generate preliminary data for grant submissions."**
>
> **Sara G.M. Piccirillo, PhD**
> **Assistant Professor, University of New Mexico Health Sciences Center, Albuquerque, New Mexico**
> 2021 AACR-Novocure Tumor Treating Fields Research Grant Recipient

IMPACT ON RESEARCH FUNDING AND WORKFORCE

In response to the COVID-19 pandemic, and to mitigate its effect on medical research in the U.S., both NIH and NCI extended deadlines of grant applications, relaxed reporting requirements, and provided flexibility on how the grant money is spent (341) (see **Steps That Helped Offset Pandemic Impact on Cancer Research**, p. 76). Although the federal government supported ongoing research and offered cancer researchers the flexibility to apply their skill set and knowledge to studying SARS-CoV-2 (13,342), COVID-19 drastically decreased fundraising opportunities for cancer-focused philanthropic research organizations (343), which provide up to half of all cancer research funding in the U.S. (332) and often fund high-risk, high-reward projects.

Progress against cancer stems from global collaborative efforts. Thus, examining the impact of the pandemic on cancer-focused research organizations around the world is instructive. For example, Cancer Research UK, a leading United Kingdom charity, which funds roughly 50 percent of all publicly funded cancer research in the country and collaborates extensively with organizations and institutions in the U.S., reduced its research budget by almost seven percent, amounting to 12 fewer fellowships, 24 fewer 5-year research programs, and 68 fewer projects (344). In its annual report published in July 2021, the organization reported a more than 11 percent drop in its fundraising income (345). Similar trends have been observed in the U.S. and Canada (344,346,347), underscoring the challenges faced by philanthropic organizations that fund collaborative cancer research worldwide.

> **"The major impact of the pandemic has been the inability to attend conferences, share our research, and learn about new developments in the field. Collaborations have also been affected by the limitations in travel, including lost opportunities for scientists and students visiting from other institutes and/or other countries."**
>
> **Ali Azhdarinia, PhD**
> **Associate Professor, The University of Texas Health Science Center, Houston, Texas**
> 2019 Neuroendocrine Tumor Research Foundation-AACR Grant Recipient

Over the past two decades, rapid advances in cancer science and medicine have transformed the cancer research community into an expansive and thriving collaborative workforce that includes researchers across the spectrum of cancer science and medicine, as well as additional disciplines across the broader fields of science, technology, engineering, mathematics, and medicine (STEMM). Impact on any one STEMM workforce ultimately impacts innovations and advances in cancer research and patient care. Data specifically evaluating the impact of the pandemic on the cancer research workforce are still emerging, but there is available information on how the COVID-19 pandemic has impacted the broader STEMM workforce, which includes the cancer research community. A survey of more than 45,000 NIH-funded researchers shows the impact of the pandemic on the medical research community; 55 percent of survey respondents said that the pandemic will have a negative impact on their career trajectory, while 76 percent reported lower levels of productivity (348).

> **"I had to learn to pivot quickly to other vendors to complete experiments when necessary. However, this change in reagents makes it difficult to assess whether small changes in the data are explained by biological or technical differences."**
>
> **Rodrigo Romero, PhD**
> **Postdoctoral Fellow, Memorial Sloan Kettering Cancer Center, New York, New York**
> 2021 AACR-Exelixis Renal Cell Carcinoma Research Fellowship Recipient

Of the many adverse effects of COVID-19 on the STEMM workforce, perhaps the most far-reaching is its impact on early-career investigators (ECI)—students (undergraduate, graduate, medical), postdoctoral fellows or medical residents, junior faculty—especially women and those belonging to underrepresented population groups. Eighty percent of early-career and 81 percent of mid-career investigators who responded to an NIH survey indicated a lower level of productivity (348). The negative impact of the COVID-19 pandemic was significantly more pronounced on female oncologists compared to their male peers. Eighty-nine percent of female oncologists indicated that the pandemic has negatively affected their personal life compared to 78 percent of male oncologists. During lockdowns, women reported increased

In January 2021, the Council on Government Relations revised its August 2020 report, *Research Impact Under COVID-19*. The revised **estimates suggest research output losses of 20-40 percent between March 2020 and February 2021**, with potential impact approaching tens of billions of dollars across the entire U.S. research enterprise (355).

time spent on hospital and laboratory tasks compared to men (53 versus 46 percent and 33 versus 26 percent, respectively), and a significantly higher proportion of women than men spent less time on science and personal care (39 versus 25 percent and 58 versus 39 percent, respectively) (349). The pandemic also exacerbated already existing disparities and created additional challenges for women with children (350). For example, mothers suffered a 33 percent larger decrease in research hours compared to fathers (351).

> **"The pandemic, including the supply chain crisis, caused significant delays in research and patient care. Although my lab was only shut down temporarily, the productivity impact will linger for years."**
>
> **Christopher D. Willey, MD, PhD**
> **Professor, University of Alabama, Birmingham, Alabama**
> 2020 AACR-Novocure Tumor Treating Fields Research Grant Recipient

In March 2021, the National Academies of Science, Engineering, and Medicine reported—based on a survey of nearly 800 women in the academic STEMM fields—the disproportionately adverse impact of the pandemic on women's research careers. According to the survey's findings, 28 percent of women reported an increase in workload or hours worked, and 25 percent stated a decrease in productivity (352). Researchers worry that the impact of the COVID-19 pandemic will likely exacerbate these disparities if left unaddressed (353,354).

Researchers belonging to underrepresented minorities (URM) are uniquely vulnerable to the disruptions caused by the pandemic. Even before the pandemic, URM researchers working in academia were less likely to receive NIH funding compared to their nonminority counterparts and thus had smaller research programs (356), increasing their vulnerability to the pandemic-related shutdown of research operations. URM researchers also share a disproportionately high burden of participating in services to their departments and institutions (357-360). There are growing concerns that URM researchers may be called upon to take on additional service burden during a period of recovery from shutdowns, thus worsening inequities and hampering their ability to focus on research (354). Because many URM researchers are more likely to engage in research pertaining to underserved populations (361,362), the non-research-related burden on their time can have a long-term effect on research of minority communities, further widening health disparities. It is critical for policy makers and the medical research community alike to develop effective approaches and accessible resources to mitigate the adverse effects of the pandemic on URM researchers.

> **"My research is based in the community, specifically in the Latino community. As the Latino community was disproportionately affected by COVID-19, recruitment of my studies was also affected."**
>
> **Francisco Cartujano-Barrera, MD**
> **Assistant Professor, University of Rochester Medical Center, Rochester, New York**
> 2021 AACR-Genentech Cancer Disparities Research Fellowship Recipient

Another concerning aspect is the limited availability or lack of job opportunities for early-stage investigators (ESI) because of the pandemic. At the onset of the outbreak, academic institutions faced unprecedented financial challenges that resulted from a precipitous decline in clinical revenue and philanthropic funding. Consequently, many institutions in the U.S. and Europe implemented freezes or slowdowns in new hirings and/or reductions in salaries (363,364). According to an analysis of advertisements on a STEMM-focused job board, faculty job openings at U.S. institutions were down by 70 percent in July-October 2020 compared to similar time frames in the previous three years (365). The ripple effect of these measures will likely persist for years and may force many ESI to either stay longer in current positions than intended or prematurely exit the cancer research workforce entirely (366). These data point to an urgent need to provide ESI, especially women and URM researchers, the necessary funding, mentorship, and support to prevent talented scientists from exiting the cancer workforce and to maintain the momentum of the impressive progress against cancer (38).

> **"The pandemic has made population-based research extremely difficult. Access to potential participants has been extremely limited, to the point that epidemiological study of cancer has been nearly impossible."**
>
> **Karl T. Kelsey, MD**
> **Professor, Brown University, Providence, Rhode Island**
> 2018 AACR-Johnson & Johnson Lung Cancer Innovation Science Grant Recipient

IMPACT ON DISCOVERY SCIENCE AND CLINICAL STUDIES

On March 13, 2020, the United States declared a national emergency in response to the COVID-19 pandemic (367), which led to most state and local governments issuing "shelter-in-place" orders (368). In response to the shutdown, academic institutions, including cancer centers, only allowed restricted access to the facilities to maintain the most irreplaceable cell lines, genetically modified model organisms, or other time-sensitive experiments; many opted to stop all experiments completely (369,370) (see **Impact of the Pandemic on Cancer Researchers: A Survey of the AACR Research Grant Awardees**, p. 55). The shutdown of laboratories forced turnover of staff, reduction of patient biospecimens, and delays and/or shortage of laboratory materials due to national lockdown restrictions and reprioritization of health systems resources, resulting in a halt of most ongoing experiments (369,371). Furthermore, the pandemic disrupted academic networking and in-person conferences, the long-standing models of productivity, innovation, and collaborations, respectively (372). Because of the interwoven nature of basic research and clinical studies (see **Figure 7**, p. 54), the shutdown also adversely affected clinical trials. The collective impact of the numerous effects of the pandemic on cancer science and medicine was captured in a survey of more than 200 cancer researchers in November 2020. The surveyed researchers estimated that their work has been set back by an average of six months and that research breakthroughs would be delayed by almost 18 months (373).

A survey conducted **between March 23 and April 3, 2020**, showed that only **20 percent** of the **institutions in the U.S.** and **14 percent in Europe** continued to **enroll patients in active cancer clinical trials at the rate** comparable to the prepandemic period (376).

Clinical trials evaluate the safety and efficacy of lifesaving anticancer therapeutics and play a pivotal role in realizing the potential of discovery science as a driver of clinical breakthroughs (374). One way to measure how COVID-19 has altered cancer science and medicine is to examine the impact of the pandemic on clinical trials. In the first half of 2020, the pandemic-necessitated lockdown measures, combined with severely strained health care systems, had an immediate adverse effect on clinical trials. In the United States, the number of patients enrolled each week in NCI-sponsored clinical trials was more than halved between early March and early April 2020 (375). Another report found that only 20 percent of the surveyed U.S. institutions were continuing to enroll patients in cancer clinical trials at pre-COVID-19 rates (376). According to one study that examined clinical trial registration on a global commercial platform, there was a 60 percent decrease in the number of new cancer clinical trials launched during the five-month period from January 2020 to May 2020, when compared to the prepandemic period (336).

> **"All lab work was postponed because traditional laboratory work is not possible when working from home. Also clinical trials stopped inclusion. All of this slowed down my early career start, and will probably affect my ability to get further grants in the coming years."**
>
> **Roger Olofsson Bagge, MD**
> **Associate Professor, Gothenburg University, Germany**
> 2021 AACR-Ocular Melanoma Foundation Career Development Award, in honor of Robert C. Allen, MD Recipient

The negative impact of the pandemic on clinical studies was multifaceted. One study found that 70 percent of survey respondents who were offered the opportunity to enroll in a clinical trial declined to do so because of the fear of increased COVID-19 exposure (377). Findings from a survey carried out between March and April 2020 show that 49 percent of institutions conducting early phase clinical trials for childhood cancers in Spain interrupted recruitment in ongoing trials. All institutions suffered personnel shortages (a 59 percent decrease in staff availability) and difficulties in enrolling patients (a 75 percent decline in patient recruitment) or monitoring activity (73 percent of trials were postponed) (378). Clinical research investigators considered concern for patient care to be a key factor in the decline in trial recruitment, closely followed by the concern for the type of cancer therapy, including route of administration (for example, whether patients needed to visit the facility for treatment) (376). In a one-year follow-up analysis (March 2021), the authors examined the collective impact of COVID-19 on cancer clinical trials around the world. Encouragingly, the total number of cancer clinical trials that had to be stopped due to the pandemic started to recover in May 2020, and the trials that were reactivated after initial suspension did so quickly, in a matter of months, regardless of the cancer type being studied (379). This recovery was, in part, because of adaptations in enrolling and treating clinical trial participants that were made in response to the pandemic (380).

> **"The COVID-19 pandemic disrupted research progress, including full shutdown of my lab for several months. In addition, as a physician, I had clinical responsibilities that precluded research activities. Overall, the COVID-19 pandemic stalled progress in generating preliminary data and advancement of my research."**
>
> **Emil Lou, MD, PhD**
> **Associate Professor, Masonic Cancer Center, Minneapolis, Minnesota**
> 2019 AACR-Novocure Tumor Treating Fields Research Grant Recipient

The quick rebound of cancer clinical trials after the first peak of the pandemic is, in part, the result of a collaborative and concerted effort among key stakeholders, including investigators, research funding agencies, and regulatory bodies, in quickly adapting to a revised workflow to minimize the adverse effects of the pandemic on this critical aspect of medical research (see sidebar on **Lessons from COVID-19 to Streamline Cancer Clinical Trials**, p. 73, and see section on **Pandemic-Related Flexibilities for Cancer Clinical Trials**, p. 76).

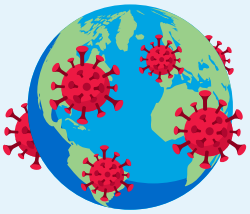
IMPACT OF COVID-19 ON THE CANCER CARE CONTINUUM

The COVID-19 pandemic has impacted every aspect of the cancer care continuum worldwide for patients with cancer, cancer survivors, and their caregivers, with some effects that are immediate and many that are long term, but currently unclear (13) (see sidebars on **Impact of COVID-19 on Cancer Care Across the Globe**, p. 59, and **Disruption of the Cancer Continuum During the COVID-19 Pandemic**, p. 61). In this section, we will discuss pronounced delays in cancer screening during the early months of the pandemic that may increase late-stage cancer diagnoses in coming years; interruptions in treatment of some patients with cancer that may have potentially life-threatening outcomes; adjustments in lifestyle that may affect the long-term physical and mental health of cancer survivors; and widened cancer health disparities that disproportionately and adversely affect racial and ethnic minorities and other medically underserved populations.

IMPACT ON CANCER SCREENING

Cancer screening is the evidence-based practice of identifying precancerous lesions or cancer in an individual before any of its

IMPACT OF COVID-19 ON CANCER CARE ACROSS THE GLOBE



COVID-19 has altered cancer care worldwide in myriad ways ranging from halting or redesigning clinical trials, interrupting cancer screening, diagnosis, and treatment to refocusing the oncology workforce to cover non-cancer-related services (381). The long-term impact of these disruptions is yet to be realized. Selected examples from around the world of the adverse impact of COVID-19 on cancer care delivery are listed below:

France

According to the electronic health records from a major health care provider in France, **new referrals for colon cancer declined by 31 percent** between March and May of 2020 compared to the average of the previous two years; surgeries for colorectal cancer declined by 34 percent over the same time period (382).

Brazil

The **average number of cancer diagnoses declined considerably** in all Brazilian regions between January and August 2020 compared to 2019, ranging from 24.3 percent reduction in the North to nearly 43 percent reduction in the Northeast region (383).

India

Between April and May of 2020, **cancer screening services were stopped or functioning at less than 25 percent of usual capacity** at more than 70 percent of health care centers in India (384).

Africa

According to a survey of cancer care providers from 23 centers in 18 countries in Africa, 30 percent of respondents reported that **new patients experienced delayed initiation of treatment** between June and August of 2020 (385).

United Kingdom

In the United Kingdom, suspected **cancer referrals decreased by 350,000** between March and August of 2020 compared to the same period in 2019 (386,387).

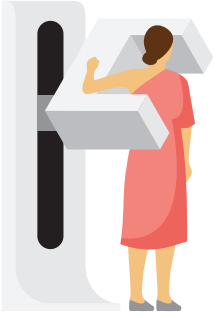
signs or symptoms appear (398). If an aberration is detected at the earliest possible time during cancer development, health care providers can make an informed decision on whether to monitor, treat, or surgically remove the aberration before it progresses to a more advanced stage.

While it is clear that COVID-19 increased the risk of morbidity and mortality in patients with cancer (see **Burden of COVID-19 in Patients with Cancer**, p. 41) (399), the full magnitude of its adverse effects on cancer care will become evident in coming years (400). In April 2020, the Centers for Medicare and Medicaid Services (CMS) recommended that individuals consider postponing nonurgent services, including preventive care visits and cancer screening examinations for colorectal, breast, cervical, and lung cancers (401). Many institutions halted cancer screening procedures, postponed nonurgent surgeries, and allocated hospital resources to COVID-19 care (402,403). Additionally, the referral cascade from the primary care for the preliminary cancer diagnosis was impaired (404). The collective outcome of these necessary measures to prevent the spread of COVID-19 was a precipitous decline in recommended cancer screening across five cancer types (see sidebar on **Impact of the COVID-19 Pandemic on Cancer Screening**, p. 62) (38,65,405-413).

With a return of cancer screening rates to prepandemic levels, there are also reports of an increase in cancer diagnoses at an advanced stage of the disease (405,406). Important lessons are emerging from these studies that can be instructive in improving future uptake of cancer screening. As one example, recovery of screening rates for colorectal cancer using noninvasive, at-home tests, such as stool-based tests, has been quicker compared to imaging-based, more invasive approaches, such as colonoscopy (407). Development of noninvasive, at-home screening tests for different cancer types may increase broader uptake of cancer screening. Similarly, there was a substantive uptake of lung cancer screening in 19 states in 2020 (during the pandemic) when compared to 2019 (before the pandemic), even though lung cancer screening did not change nationwide (408). A closer and careful examination of the underlying reasons that led to an increase in lung cancer screening in these states may help in devising plans to encourage routine screening in individuals at risk of developing lung cancer.

Continued on page 61

Experts recommend patients delay breast cancer screening by four to six weeks after getting vaccinated, in close consultation with their health care providers. This is because studies have found that, like other vaccines, **COVID-19 vaccines can cause swollen lymph nodes** (278), which can affect interpretation of imaging results, especially in mammograms that are used to screen for breast cancer.



WENORA JOHNSON
Age: 55 | Joliet, IL

Diagnosis of Precancerous Polyps After Pandemic-Related Delay in Colonoscopy

Wenora Johnson, 55, knows the importance of routine cancer screening and preventive measures all too well. Wenora, who lives in Joliet, Illinois, has Lynch syndrome, an inherited condition that predisposes her to certain types of cancer. So, while missed or delayed cancer screenings caused by the pandemic were problematic for many, the four-month delay for Wenora was potentially life-threatening.

In the past, Wenora's colonoscopies, while important annual checkups because of her Lynch syndrome, had not found anything.

"This was different. It came back with three precancerous polyps," she said. "It really brought home to me the effects of what COVID has done. It made me realize just how important these scans are—they're lifesaving for me."

Wenora was first diagnosed with colorectal cancer in 2011, and then, after genetic testing, with Lynch syndrome. Then, she was diagnosed with early-stage endometrial cancer when, in consultation with her health care team, Wenora opted for a hysterectomy as a preventive measure to reduce her chances of cancer.

"That was really a wake-up call that I cannot take for granted this Lynch syndrome diagnosis," she said.

"There are some days I feel like I'm living on borrowed time because I don't know when the next cancer is going to rear its ugly head. But at the same time, I have this comfort of knowing that I'm being proactive by continuing to get screened for cancer every six months.

"Another important thing that I've shared with my family, especially my two young-adult children, is that it's so important to stay on top of it. It's lifesaving," she added.

Since her initial diagnosis of colorectal cancer, and in addition to the endometrial cancer, Wenora has been diagnosed with basal cell carcinoma, a type of skin cancer. Being diagnosed with three different types of cancer within a decade led Wenora to become strong advocate for genetic testing and routine cancer screening.

"For me, genetic counseling that follows a genetic test will help you determine what changes you need to make in your life," she said.

Wenora's approach to being vigilant about cancer screening extended to implementing preventive measures during the pandemic. She is extremely careful to follow the recommendations of her health care team—washing hands, minimizing unnecessary contact with others, and masking up.

And she found that she loved the electronic portal she used to communicate with her health care team. The portal has become a powerful tool that enables her to keep up with her reminders, not only for her regular cancer screenings, but also for vaccination against influenza and now, COVID-19.

She has been fully vaccinated against COVID-19 and feels that it will minimize her risk and is an important part of her heath care regimen.

"I encourage others to do the same, especially if you have a compromised immune system. And if you suffer from cancer, that's one less worry," Wenora said.

She is thankful that she was on maintenance anticancer treatment and regular surveillance for cancer. Ever since her diagnosis of Lynch syndrome, the importance of cancer research and federal funding of that research has become personal for Wenora.

"Research is coming up with new and innovative ways to treat cancer. It's important because my children have a 50 percent chance of getting Lynch syndrome and then passing it on to their children. So, it's so imperative that the future is bright," Wenora emphasized.

DISRUPTION OF THE CANCER CONTINUUM DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic has caused unprecedented disruptions across the cancer continuum. The negative effects of some of these disruptions are immediately apparent, while others may take years to become clear:

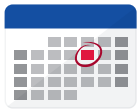
Cancer Etiology

Involvement of some cancer-causing genes and proteins in SARS-CoV-2 infection has led to the hypothesis that long COVID—lingering symptoms of the disease in some patients months after exposure—may accelerate cancer onset and progression in COVID-19 patients with no history of cancer (388). Long-term and carefully designed studies are required to determine whether long COVID in fact impacts cancer development.

Cancer Prevention

The pandemic increased tobacco (389,390) and alcohol (391) use and decreased physical activity (392,393), all modifiable behaviors with key roles in cancer prevention.

Cancer Detection



The pandemic resulted in nearly 10 million missed cancer screenings from January 2020 to July 2020 (394).

Cancer Diagnosis

The pandemic impaired referrals for preliminary cancer diagnoses and led to an 11 percent increase in patients diagnosed with inoperable or metastatic cancer during March-December 2020, when compared to the same time frame in 2019 (395).

Cancer Treatment

The pandemic necessitated adaptations in anticancer treatment regimens, ranging from canceled surgeries and radiotherapy to modified schedules and/or dosing for patients receiving chemotherapy, molecularly targeted therapy, and/or immunotherapy (396).

Cancer Survivorship

The pandemic provided a new source of stress for cancer survivors, compounding the many mental health symptoms, such as anxiety and depression, already prevalent in this population (397).

There is suboptimal uptake of cancer screening among those individuals who should get screened (38,65). Furthermore, there are well documented disparities in the uptake of cancer screening among racial and ethnic minorities and other medically underserved segments of the U.S. population. These challenges have been exacerbated in the past two years due to the ongoing COVID-19 pandemic (410,411), which led to a sharp decline in cancer screening during its initial peak. Additionally, historic injustices caused by the health care industry may be responsible for reducing trust and participation in cancer screening among racial and ethnic minorities (418-420), especially against the backdrop of the pandemic. It will be important to implement strategies, such as culturally appropriate, clear, and simple messaging and community outreach, to restore trust in health care professionals. Equally important will be coordinated and concerted efforts to raise awareness of the importance of cancer screening in individuals who should routinely receive the U.S. Preventive Services Task Force (USPSTF)-recommended cancer screening.

Cancer screenings that were delayed or missed because of halted preventive services during the first half of 2020 have already been followed by diagnoses of early-stage cancers in patients like **Wenora Johnson** (see p. 60) and **Senator Amy Klobuchar** (see p. 80). Researchers are increasingly concerned that missed cancer screening will lead to an increase in cancer diagnoses at an advanced stage and decreased cancer survival in the coming years (225,421). Two recent models from the UK reported a more

IMPACT OF THE COVID-19 PANDEMIC ON CANCER SCREENING

The U.S. Preventive Services Task Force (USPSTF) is an independent volunteer panel of experts in prevention and evidence-based medicine. The panel carefully reviews the available data and weighs the risks and benefits for the broader population before issuing cancer screening guidelines. Currently, there are USPSTF guidelines for five types of cancer, four of which apply to individuals who are at an average risk of developing breast, colorectal, prostate, or cervical cancer. Guidelines for lung cancer apply to individuals who are at a high risk of developing the disease because of current or past tobacco smoking. Screening rates for all five cancers declined significantly during the peak of the pandemic, although more recent data suggest that screening rates for some cancer types are returning to prepandemic levels:

Breast Cancer

USPSTF Recommendation: Mammogram every other year for women ages 50-74.

COVID-19 Impact: An **87 percent decline** was observed in breast cancer screening in April 2020 compared to the average for the same month over the previous five years (414).

Cervical Cancer

USPSTF Recommendation: Cervical cytology every three years for women ages 21-65; high-risk human papillomavirus testing alone, or in combination with cytology, every five years for women ages 30-65.

COVID-19 Impact: An **84 percent decline** was observed in cervical cancer screening in April 2020 compared to the average for the same month over the previous five years (414).

Colorectal Cancer

USPSTF Recommendation: Stool-based tests every 1-3 years, and/or imaging-based tests every 5-10 years, for all adults ages 45-75.

COVID-19 Impact: An **80 percent decline** was observed in colorectal screening from March 18, 2020, to May 4, 2020 compared to the period from January 29, 2020, to March 17, 2020 (415).

Lung Cancer

USPSTF Recommendation: Low-dose computed tomography (LDCT) every year for all adults ages 50-80, who are current smokers or who quit within the past 15 years, with a 20 pack-year smoking history.

COVID-19 Impact: Although some reports have shown a decline, a large, population-based study showed **no significant change** in uptake of lung cancer screening between 2019 and 2020 (408). It is important to note that the uptake of LDCT was suboptimal even before the pandemic (416).

Prostate Cancer

USPSTF Recommendation: Periodic prostate-specific antigen-based test, as recommended by the health care provider, for men ages 55-69.

COVID-19 Impact: A **36 percent decrease** was observed in prostate cancer screening in April 2020 compared to April 2019 and April 2018 (417).

Variable Recovery of Screening Rates

Recent evidence indicates that cancer screening rates are rebounding to prepandemic levels. As one example, one study compared screening rates for breast and colorectal cancer among commercially insured American adults before and after March 13, 2020. Findings showed that screening rates for breast cancer have recovered almost completely (88 per 10,000 beneficiaries before March 2020 versus 88 per 10,000 beneficiaries in July 2020), while for colorectal cancer, the screening rates are on an upswing but have not yet fully recovered (15 per 10,000 beneficiaries before March 2020 versus 13 per 10,000 beneficiaries in July 2020) (413).

Sixty-six percent of radiation oncologists said existing patients with cancer experienced **interruptions in treatment with radiation due to the pandemic**, according to a survey conducted between January 15 and February 7, 2021 (406).

than five percent increase in cancer mortality risk with the late diagnoses and the delayed referrals during the pandemic (404). Other modeling studies further predict increased rates of advanced cancer diagnoses, as well as higher morbidity and mortality due to decreased and delayed cancer screening in 2020 (422,423). Concerns of cancer diagnoses at advanced stages are reinforced by findings of a survey—conducted between January 15 and February 7, 2021—of radiation oncologists, medical professionals who utilize radiation-based methods to treat cancer. Two-thirds of the respondents said that new patients are presenting with more advanced-stage cancers and 73 percent of physicians noted that patients are not receiving recommended cancer screenings (406). One study found that circulating tumor DNA, a biomarker for assessing tumor burden, was much higher in patients who were diagnosed with colorectal cancer after the pandemic-associated lockdown (424). The global nature of this concern is underscored by a study from Japan that found that patients with gastrointestinal cancer were diagnosed at an advanced stage during the COVID-19 pandemic (425). An increase in cancer diagnoses at an advanced stage may result in increased cancer morbidity and mortality in the coming years (409). It is critical to continue monitoring whether the substantial decrease in cancer screening leads to any long-term changes in U.S. cancer mortality (412,413).

IMPACT ON CANCER TREATMENT

The cancer treatment paradigm is built on five "pillars," namely, surgery, radiotherapy, chemotherapy, molecularly targeted therapy, and immunotherapy (38). Most respondents to surveys of patients with cancer—conducted early during the pandemic—indicated that they were at least moderately worried about the impact of delays in their cancer care (426,427). Later evidence suggested that preventive measures to contain the pandemic resulted in interruptions across all pillars of the cancer treatment paradigm (see sidebar on **Impact of the COVID-19 Pandemic on Cancer Treatment**, p. 65).

Pandemic-related interruptions in treatment of patients with cancer, such as **Federico de Armas Heinzen** (see p. 64), were reported worldwide, and across different types of cancer and treatments. One study from Canada found that 57 percent of patients with lung cancer experienced changes in their treatment plans between March 2 and May 30, 2020, as a direct result of the pandemic. Most changes encompassed either a delay (nearly 40 percent) or cessation (almost 15 percent) of palliative chemotherapy, while 26 percent of changes occurred in dosing and schedule of anticancer treatment (429). According to a prediction model based on data from the United Kingdom, a six-month delay in surgery because of the pandemic could cause more than a 30 percent reduction in five-year survival of patients who had an advanced cancer of the lung, pancreas, or ovary (403). These concerning predictions are compounded by findings of a September 2021 report that clearing the backlog of cancer treatment and referrals could take over a decade (430). Similar troubling patterns are emerging in the U.S. For example, researchers predict that there will be nearly 2,500 additional deaths related to breast cancer because of the delays in cancer care caused by the pandemic, and if these delays are extended for 12 months, breast cancer-related deaths will likely double (431).

It is important to note that the full extent to which the modified cancer care, including changes in treatment regimen necessitated by the pandemic, will affect long-term survival and quality of life of patients with cancer remains unclear. A few recent studies analyzing effects of delayed or revised cancer treatments on clinical outcomes for patients with cancer indicate that some of the modified treatment schedules have not had an adverse effect on clinical outcomes for patients with cancer and may, in fact, result in positive effects on their physical, psychological, and financial health (432) (see **Rethinking Cancer Treatments**, p. 73). Carefully designed and executed long-term studies, such as the NCI COVID-19 in Cancer Patients Study (NCCAPS) (433), will provide valuable insights into any lasting impact of the pandemic on cancer patients and survivors.

IMPACT ON CANCER SURVIVORSHIP

Clinical breakthroughs across the continuum of cancer care are saving lives and helping individuals live longer and fuller lives after a cancer diagnosis. The number of cancer survivors has increased from 1.4 percent of the U.S. population in 1971 to more than five percent in 2019 and is projected to account for nearly seven percent of the U.S. population by 2040.

Cancer survivorship is a broad term used to capture a wide range of unique experiences of living with, through, and beyond cancer. These experiences are defined by the type and stage of cancer, the age at which an individual is diagnosed, and the treatment a patient with cancer is receiving. Experience with cancer can cause a range of strains on an individual that include

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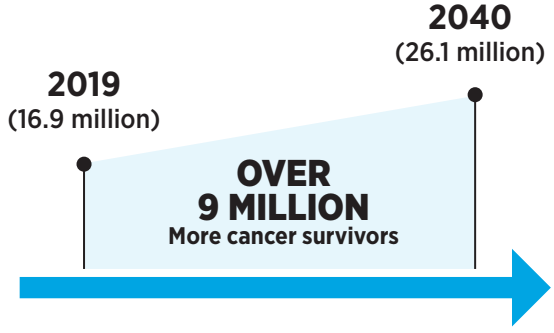
U.S. CANCER SURVIVORSHIP AT A GLANCE



In **2019**, there were **16.9 million cancer survivors** living in the United States. The number is estimated to increase by **over 9 million by 2040**.

FEDERICO DE ARMAS HEINZEN
Age: 51 | Mexico City, Mexico

Managing Metastatic Melanoma Despite an Interruption in Treatment Because of COVID-19

In 2015, Federico de Armas Heinzen felt a swollen lymph node under his right arm and it concerned him. Federico was initially diagnosed with melanoma in 2005 and, for a decade, had no signs of the cancer recurring.

So, Federico—a Uruguayan living in Mexico City, Mexico, with his wife and young daughter—contacted Antoni Ribas, MD, PhD, FAACR, a physician-scientist specializing in melanoma and immuno-oncology at the University of California, Los Angeles (UCLA), California.

"When Federico contacted me, he had developed metastatic melanoma that had spread to his eye, bones, adrenal gland, and multiple lymph nodes," Dr. Ribas said. "He and his wife wrote to me that they didn't have any treatment options in Mexico and asked if we have any ongoing clinical trial or treatment option," Dr. Ribas recalled.

At the time, UCLA was part of a phase I clinical trial to test the efficacy of two molecularly targeted therapeutics against BRAF and MEK—two proteins that drive the growth of several types of cancer—combined with immunotherapy to treat patients with melanoma, an idea that had come from years of research.

Federico qualified and was able to participate in that trial.

"I knew that the distance was a problem, but I also knew that this was the best possible option he may have," Dr. Ribas remembered.

Although the molecularly targeted inhibitors could be taken orally, the immunotherapeutic had to be administered by infusion. So, for Federico, participating in the clinical trial required trips from Mexico City to UCLA every two weeks. In addition, the clinical trial required routine blood tests and scans to monitor his response to the treatment. Federico started to respond to the treatment.

"When I started the treatment in January 2016, the cancer had spread in my body. By the end of July, I was clean," recalled Federico, as his nurse prepared him to receive his immunotherapeutic by infusion.

"I have 30 minutes to get the medicine to my blood, and it's magical, you know, because it works," Federico chuckled.

In March 2020, when the pandemic hit and the United States implemented strict travel restrictions to minimize the spread of COVID-19, Federico was unable to come to Los Angeles for his biweekly treatments.

Not only was Federico unable to come to UCLA for infusions of the immunotherapeutic, but he also lost his access to the molecularly targeted therapeutics, oral medications that were provided to him during his visits to UCLA.

"For five months, he was not able to come and continue on the clinical trial. That's troublesome because we knew the treatment was keeping his melanoma under control," Dr. Ribas said.

"COVID-19 really affected him and really affected all of us because we knew it was hard to deliver the care to him with all of these disruptions," he added. "After things started to improve, we went from doing it all in person to doing video visits and were able to ship drugs to him, which was not allowed before the pandemic. That's one of the things that I hope will be carried on after the pandemic when we go back to normal business."

Despite the new ability to mail the molecularly targeted therapeutics to him, Federico was still missing the infusions of the third medication in the trial, the immunotherapeutic that had to be administered by infusion at UCLA. Federico couldn't come back to UCLA for in-person visits until October 2020.

"It was really nerve-racking for all of us. It was very hard to know that you have a patient to whom you can't deliver the treatment that had been benefiting him," recalled Dr. Ribas.

Unfortunately, while Federico was dealing with interruption in his cancer treatment, his scans showed he had developed a brain tumor that was independent of his melanoma. So, in the midst of a pandemic and an interrupted treatment for his melanoma, Federico had to undergo radiation therapy to treat his brain tumor.

"That was really tough. When you have these metastases in your body, it's hard to face," recalled Federico.

Federico's health care team advised him to get vaccinated for COVID-19 as soon as possible, and he did so when he was able to travel to UCLA.

"You have other patients and these people that take care of us. I needed vaccination for that reason. And for me," Federico said.

Although he feels it's not the same as an in-person visit, Federico is also grateful that he was able to keep in touch with his health care team at UCLA via telemedicine.

"At least you have the support from them, you know, whatever it should be," Federico added.

IMPACT OF THE COVID-19 PANDEMIC ON CANCER TREATMENT

Preventive measures to limit the spread of COVID-19 had an immediate, wide-ranging, and negative impact on multiple aspects of cancer treatment, as underscored by the examples below:

64% to 87%	64 to 87 percent of patients with cancer reported **delays in their planned surgery** during the height of the pandemic compared to prepandemic levels.
8 to 45 days	8 to 45 days of **delay in radiotherapy** were reported by patients with cancer during the height of the pandemic compared to prepandemic levels.
36% to 51%	36 to 51 percent of cancer centers reported a change in **treatment plan for chemotherapeutic agents** during the height of the pandemic compared to prepandemic levels.
95% reduction	95 percent **reduction in biopsies** was observed during the height of the pandemic compared to prepandemic levels.
31% to 56%	31 to 56 percent of oncologists reported a **change in schedule for immune checkpoint treatment** during the height of the pandemic.
18% to 48%	18 to 48 percent of physicians and ministries of health reported **interruption of palliative care** during the height of the pandemic compared to prepandemic levels.

Developed from (428).

physical, psychosocial, and financial stresses and can often also disrupt the lives of family members, friends, and other caregivers (434-436). The COVID-19 pandemic and associated preventive measures have caused additional stress in the lives of many cancer survivors, their family members, friends, and other caregivers.

Evidence is accruing of the negative impact of the pandemic on the mental and physical health of cancer patients, survivors, and caregivers arising from social isolation, financial stress, food insecurity, concerns about timely access to cancer treatments, and disease recurrence (205,245,437-441). As an example, most participants in an Internet-based survey reported social isolation (76%) and worsening mental health impact (70%) since the beginning of the COVID-19 pandemic, with food insecurity and financial hardship correlating significantly with adverse mental health impact (442). In a survey administered in late May 2020, 53 percent of patients with a cancer diagnosis who completed the survey reported experiencing loneliness, which is an independent risk factor for early mortality (443), as well as more severe symptoms of anxiety, depression, fatigue, sleep disturbance, cognitive dysfunction, and pain (444). Another study found that the alarmingly high rates of stress and stress symptoms in cancer patients and survivors are comparable to those of noncancer patients who have post-traumatic stress

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In cancer science and medicine, adolescents and young adults (AYA) are individuals between the ages of 15 and 39. **About 89,000 AYAs are diagnosed with cancer each year in the U.S.** (447). Because individuals in this age group are only at the start of their personal and professional lives, a cancer diagnosis poses a unique set of psychosocial and financial challenges (38).

RACHEL ORTH
Age: 33 | Arlington, TX

Navigating a Clinical Trial for Metastatic Gastric Cancer During the Pandemic

During Rachel Orth's annual well-woman checkup in November 2020, a mass was discovered on her ovary. Rachel's doctors scheduled a surgery for December to remove what they thought was a benign tumor.

The surgery, however, revealed that Rachel had cancer. She was 33 years old with three young children.

"Because of COVID, I was only allowed to have my husband with me in the hospital," Rachel explained. "He was in the waiting room by himself, so he was the one who had the first conversation with my doctor when she told him that the biopsies had shown cancer. When I was moved to my room, he was waiting for me, and he was the first one to tell me that it was cancer."

Learning that she had advanced gastric cancer was overwhelming, an experience only compounded by the pandemic.

"Suddenly my life went from school drop-offs and pickups, taking care of my preschooler, going grocery shopping, and taking care of my family to a lot of doctors' appointments, scans, infusions, and not feeling well and having to rely on a lot of people for help," she said. "And during COVID-19, that was really difficult. I think cancer is probably the most isolating experience of my life. Going through that during the pandemic, which is another very isolating experience, was traumatizing."

Rachel's first oncology appointment was conducted on Zoom.

Rachel and her husband used the weeks of recovery following her surgery to seek additional expert opinions. Advised that her best option was to pursue clinical trials, she opted to go to the University of Texas MD Anderson Cancer Center in Houston, some 270 miles away from her home in Arlington, Texas.

Before joining a phase I clinical trial at MD Anderson, Rachel needed to undergo a series of procedures—an endoscopy, a colonoscopy, and a laparoscopy. But before she could start treatment, her husband became symptomatic with COVID-19.

"When he tested positive, I immediately contacted my team and let them know; they had me get tested and I was negative, but I had to quarantine," she said.

As a result, Rachel's medical procedures were delayed by two weeks.

"Then I started running a fever and became symptomatic which meant postponing the appointments again, which feels like a long time when you've been given a really poor prognosis of months to a year to live," said Rachel.

After a month Rachel was able to undergo the needed procedures and enter the clinical trial, but once again she felt the impact of the pandemic.

"My husband was allowed to video call in for my appointments, but I was on campus alone going to my scans, blood work, and doctor appointments all by myself," she said. "Sometimes I was in that room alone, going through the protocols. There was a lot of anxiety; I was processing this whole new world of terminal cancer. It was very scary."

Rachel's metastatic gastric cancer has responded well to the trial. She goes to Houston every three weeks for treatment.

"My scans have shown that the disease is stable and we're really thankful for that," said Rachel.

As a result, she is able to care for her children and is thankful to be able to do all the things that she likes to do with them.

"I'm going on a field trip with my daughter tomorrow to a tree farm. She's so excited," Rachel said in a recent interview.

Rachel strongly believes that funding for cancer research needs to be a priority. Only with robust and sustained funding for medical research will scientists be able to develop newer and better treatment options for patients with advanced disease like her.

"I think that funding for cancer treatments, especially late-stage treatments, is really critical because it is life-sustaining for me," she said. "Right now, I'm alive because of the treatment that I have. Being part of that phase I clinical trial is what is keeping my cancer stable. It is what's giving me hope for the future."

disorder, for example, war veterans (445). Long-term effects of COVID-19, such as respiratory symptoms and fatigue, affect more than 15 percent of cancer survivors, who have contracted COVID-19, and adversely affect their survival and clinical outcomes after recovery (446).

The pandemic-related challenges are also apparent, and in some cases worse, in pediatric and adolescent and young adult (AYA) patients with cancer, such as **Rachel Orth** (see p. 66) and **Allyson Pile** (see p. 68), who face a unique set of challenges from cancer diagnosis and treatment, including long-term cancer care, with a prolonged monitoring for recurrent disease and long-term complications that can arise from cancer treatments (38,448,449). For example, younger patients with breast cancer experienced more delays in their cancer care during the pandemic compared to older patients (450). Long-term cancer care in this population is a key contributing factor to financial toxicity; i.e., the financial burden cancer survivors face from out-of-pocket payments, uncovered treatment-related expenses, and lost income and productivity due to treatment-related employment disruptions and symptoms such as fatigue (451). Across cancer types, financial toxicity may result in poorer quality of life (452). Cancer survivors, especially those belonging to the AYA age group, may have higher vulnerability as they face financial hardships from both the pandemic and their cancer care (453). In one survey of AYA cancer survivors, two thirds of the respondents reported experiencing at least one negative economic impact of COVID-19, such as increased credit card debt, and 71 percent reported engaging in at least one medical cost-coping behavior, such as not filling a prescription (454).

IMPACT ON CANCER HEALTH DISPARITIES

Cancer health disparities are adverse differences in cancer experienced by certain segments of the U.S. population, such as the number of new cancer cases and deaths, cancer-related health complications, decreased quality of life after cancer treatment, financial burden, screening rates, and stage at diagnosis (455). The underlying causes of cancer health disparities are multifactorial and include limited access to health care, structural and social determinants of health, racism, and discrimination. The COVID-19 pandemic has exacerbated these baseline inequities (65).

An examination of electronic health records of more than 73 million patients across the 50 states of the U.S. revealed that Black patients with a recent cancer diagnosis were at significantly higher risk of COVID-19 infection (see section on **Disparities in the Burden of COVID-19 Among Certain U.S. Populations**, p. 20). Compared to individuals who are white, Black patients with breast or prostate cancer were at more than five times higher risk of COVID-19 infection. Furthermore, compared to those who are white, the risk of COVID-19 infection was more than three times higher for Black patients with colorectal cancer, and more than two times higher for Black patients with lung cancer or non-Hodgkin lymphoma (210). Because both cancer (38,65) and COVID-19 are risk factors disproportionately affecting racial and ethnic minorities and other medically underserved populations, additional studies are needed to establish whether both risk factors are additive in increasing pre-existing health disparities.

Another study of patients with gynecologic cancer and COVID-19 in a New York City area hospital system found that Black patients were more likely to require hospitalization compared to non-Black patients (71.6 percent versus 46 percent, respectively) (456). Cancer screening declined significantly during the first half of 2020 (see **Impact on Cancer Screening**, p. 58). The reduction in cancer screening was even more noticeable for racial and ethnic minorities and those belonging to medically underserved populations of the U.S. For example, researchers found that the breast cancer screening decline in Washington state during April-December 2020 compared to the same time frame in 2019, was significantly more pronounced for women who were Hispanic (a 64.2 percent decrease), American Indian/Alaska Native (a 60.9 percent decline), Native Hawaiian or Pacific Islander (a 54.5 percent reduction), or Black (a 53.9 percent drop) compared to women who were white (a 49.2 percent decrease) (457).

In a large multi-institutional study, a 90.9 percent lower rate of prostatectomies—surgery to remove the prostate gland completely or partially—was observed among Black patients with prostate cancer compared to a 17.4 percent lower rate of prostatectomies among white patients during the initial wave of the COVID-19 pandemic (458).

Cancer health disparities impact medically underserved populations of the U.S. beyond cancer diagnosis and treatment and extend well into cancer survivorship. More than 40 percent of Black cancer survivors enrolled in the Detroit Research on Cancer Survivors study, who responded to a survey in the first half of 2020, reported feeling depressed, anxious, and/or isolated during the COVID-19 pandemic (459). Socioeconomic status is another major contributor to financial toxicity, i.e., financial distress directly related to cancer diagnosis, treatment, and management (460). In a telephone-based survey of 100 women with gynecologic cancer between March 15, 2020, and April 15, 2020, researchers found that patients who had an annual income of less than $40,000 were significantly more worried about future finances, and the pandemic-related delay in medical care resulted in a four-fold increased rate of anxiety (461).

All stakeholders must build upon the concerted efforts to learn from and address disparities exposed by the COVID-19 pandemic and use this knowledge to eliminate all health disparities, including disparities caused by cancer. As the cancer research community recovers from the COVID-19 pandemic, it is more important than ever to invest in cancer health disparities research, including community outreach, education, and engagement efforts.

ALLYSON PILE
Age: 33 | Los Angeles, CA

Accessing a Clinical Trial for Stage IV Medullary Thyroid Cancer During the Pandemic

For Allyson Pile, it was scary to receive an advanced-stage cancer diagnosis at the age of 29 and participate in a clinical trial for an experimental therapeutic. But confronting the pandemic lockdown and social isolation needed to keep her safe was terrifying.

"I am an extrovert. I get my fuel, my joy, and my energy from people," Allie explained. "After my surgery, I spent about nine months home, away from everyone. It broke my spirit to have everything that makes me happy torn away because I was immune compromised…it was excruciating."

Just as her life was returning to some normalcy, the COVID-19 pandemic hit in the United States and the Tujunga neighborhood of Los Angeles, California, where Allie lives with her mother.

Allie was initially diagnosed in 2018. During her boxing workouts with a friend, she felt the strap of her sports bra scraping over a bump on her neck. Allie ignored it until her friend became concerned and took her to an urgent care center to have it checked.

Later that day, they were at work when Allie got a call back from the urgent care center asking her to come back for some scans.

"I think I knew this was pretty serious," she said. "I ended up going to my mom's office at YMCA and tried to pretend everything was fine. She just asked how I was doing, and I broke down."

Allie's family is close-knit, and her bond with her younger sister Audrey is particularly strong. Her mother and sister were with her when her doctor told her she had cancer.

"I remember feeling my sister and her presence in that moment," she said. "I watched my mom tear up and I don't remember the last time I had seen that happen. But the biggest part I remember was my sister. And just knowing this is going to change everything."

And everything changed.

It took time to confirm the diagnosis because medullary thyroid cancer is rare, especially for someone as young as Allie. During the surgery to remove the cancer, Allie's team found that the cancer had spread. She had stage IV disease.

Deborah J. Wong, MD, PhD, has been Allie's oncologist since she was initially diagnosed.

"Allie started on the clinical trial a year before the pandemic lockdown," Dr. Wong said.

When the lockdown hit, however, everything was thrown into chaos. The clinical trial procedures required in-person testing, which made it challenging to keep Allie and others in the clinical trial, as well as all other patients, safe from COVID-19 on the large UCLA medical campus.

After the initial scramble, Dr. Wong and Allie's team performed most of her assessments via telehealth visits and moved required scans and tests to a smaller, less crowded satellite campus closer to Allie's home.

"Our research team worked very hard to get the drugs shipped directly to Allie in a safe way that maintained all the clinical trial regulations and safeguards," Dr. Wong said.

"Even when cancer patients are surrounded by family and friends, it can be very lonely," she said. "Allie is a young woman going through a serious diagnosis and treatment. Her life path is so vastly different than any of her peers, and so, apart from the pandemic, it can be really difficult."

In October 2021, for the first time in about 18 months, Allie was able to have an in-person visit with Dr. Wong. Unfortunately, scans had shown that one of Allie's tumors was growing again and the visit was to decide the next steps of her treatment.

"When she told me to come in, I knew that something was amok," Allie said.

Despite this setback, Allie believes that research has made an important difference in the quality of her life.

"For someone with her whole life in front of her, I had all these plans and dreams, and they all came to a screeching halt," Allie said. "But because of the research that's been done, I get to live. And I remember I could be in a wheelchair, or in a hospital bed for good, or getting chemo for eight hours a day. It just could look very different than it does for me because of the research that's been done."

FUTURE OF CANCER SCIENCE AND MEDICINE BEYOND COVID-19

In this section, you will learn:

- COVID-19 accelerated adoption of telemedicine across the cancer care continuum. Lessons learned from telehealth during the pandemic offer a blueprint for broader and permanent implementation of telemedicine, with potential to improve patient care and reduce physician burnout.
- Changes to clinical trials that ensured continuity of lifesaving clinical studies have the potential to improve and decentralize the design of clinical trials, with the potential to increase patient participation and minimize the time it takes to safely test anticancer therapeutics.
- The pandemic necessitated modifications in cancer treatment regimens, such as increased time between doses, with the potential to improve overall patient survival.
- Worldwide scientific collaborations and rapid sharing of resources and expertise among all stakeholders offer a framework for rapidly responding to future public health crises of this magnitude.

Evidence presented in the preceding chapters, including the powerful personal stories of patients dealing with challenges of cancer in the midst of the COVID-19 pandemic, underscores the many adverse effects of the pandemic on cancer research and patient care. Some of these effects, such as a sharp decline in cancer screening during the early months of 2020, have been quantified, while others, such as the long-term effect of missed cancer screenings on overall cancer morbidity and mortality, need to be continually monitored. Despite the many challenges posed by the COVID-19 pandemic, the success of some of the adaptations to mitigate the adverse effects of the pandemic underscore key lessons and provides future directions for cancer science and medicine. In this section, we highlight key adaptations that, if permanently implemented and further improved, may have far-reaching positive outcomes.

IMPLEMENTING TELEMEDICINE

According to NCI, telemedicine, also called telehealth, is the delivery of health care from a distance using electronic information and technology, such as computers, cameras, videoconferencing, satellites, wireless communications, and the Internet (see sidebar on **What Is Telemedicine?**, p. 70) (462). On March 20, 2020, CMS issued a regulatory flexibility that expanded coverage for telehealth services to Medicare beneficiaries (463). The use of telemedicine by the elderly and patients with cancer has already had a widespread positive effect on the delivery of oncology services during the pandemic and has allowed patients, such as **Federico de Armas Heinzen** (see p. 64) and **Rachel Orth** (see p. 66), to continue receiving cancer care, even when they are unable to visit a health care facility in person. The benefits of this strategy became immediately obvious and were reinforced by the rapid implementation of several additional regulatory waivers (see **Telehealth Policies During COVID-19 and the Impact on the Cancer Care Continuum**, p. 79). However, it is imperative that the telehealth policies enacted during the pandemic are made permanent to ensure sustained adoption and broad implementation of telemedicine for patient care (see **The AACR Call to Action**, p. 83).

Telemedicine has a long history in health care (464), and in cancer care (465,467). However, the COVID-19 pandemic has accelerated adoption of telemedicine as a key preventive measure to minimize the spread of COVID-19 and to protect patients, especially those who are immunocompromised, including patients with cancer (see sidebar on **Adoption of Telemedicine by Patients with Cancer During the COVID-19 Pandemic**, p. 71) (467). According to a July 2021 analysis, telemedicine utilization is 38 times higher than before the pandemic (468). A nationwide public opinion poll, conducted between March 26 and April 5, 2021, revealed that most Americans welcomed the expansion of telehealth. Thirty-eight percent of survey respondents had used telehealth services since the start of the pandemic, and 43 percent of the telehealth users said they want to continue using telehealth services when the COVID-19 pandemic is over (469). Other studies have reported similar findings (470).

Researchers are also using telemedicine to deliver palliative care interventions, such as exercise, to cancer survivors. One study found that adherence to exercise-based interventions among

WHAT IS TELEMEDICINE?

According to NCI, telemedicine, also called telehealth, is the delivery of health care from a distance using electronic information and technology, such as computers, cameras, videoconferencing, satellites, wireless communications, and the Internet. Telemedicine can be **synchronous**, i.e., a two-way audiovisual conversation between a patient and a provider, or **asynchronous**, i.e., transmission and presentation of a recorded health history to a health care provider.

Types of Telemedicine

Teleconsultation

Presentation of a patient's health report by the primary health care provider(s) to an expert in another institution.

Teleinterpretation

Interpretation of a patient's test results, such as images obtained from a full-body scan, remotely.

Telesupervision

Presentation of a patient's information via shared screen electronically—either recorded or with patient present in person—to a senior clinician by a medical trainee (e.g., medical student) or other health care worker (e.g., nurse) using electronic means, such as PowerPoint slides.

Telediagnosis

Remote or concurrent transmission of results from physical exams, scans and/or lab tests to a specialist, such as a pathologist, for diagnostic purposes.

Televisit

Usual visit of a patient with his or her health care provider, but using videoconferencing software.

Telemonitoring

Signs or symptoms, as well as health records, of a patient communicated to a health care team by an electronic communication platform that is compliant with the Health Insurance Portability and Accountability Act (HIPAA).

Potential Benefits of Using Telemedicine

- **Increased access to health care** Allows access to health services that may not be available to patients locally.
- **Improved health care outcomes** Promotes continuity of care regardless of the location of the patient and the provider, thus improving overall health outcomes.
- **Decreased infectious exposure** Helps avoid exposure to infectious viruses, bacteria, and other pathogens.
- **Reduced costs and/or work-related adjustments** Saves time and money by eliminating the need to travel to the health care facility or to take too much time off work or to arrange for elder- and/or childcare.
- **Facilitated caregiver and family engagement** Allows caregivers and other family members to join, which can facilitate patient care.

Potential Drawbacks of Using Telemedicine

- **Widened health care disparities** Infrastructure that enables electronic communications, such as broadband Internet, computers, or smart phones, as well as digital literacy, are two key requirements for implementing telemedicine effectively. However, lack of access to both is disproportionately experienced by patients from medically underserved populations (including, but not only, those belonging to racial or ethnic minorities, those who are old, those with disabilities, or those living in remote rural areas) and may widen already existing disparities.
- **Rapidly changing policies and reimbursement rules** The fast-paced nature of telemedicine may make it harder for health care providers to keep up with health care laws, reimbursement policies, and privacy protections.
- **Costly initial implementation** Implementing telemedicine at a health care facility, including restructuring information technology staff, purchasing necessary equipment, and training clinicians and support staff, takes time and costs money.
- **Security of personal health data** The security of personal health data transmitted electronically is also a concern, which can be mitigated by employing a HIPAA-compliant telemedicine platform.

ADOPTION OF TELEMEDICINE BY PATIENTS WITH CANCER DURING THE COVID-19 PANDEMIC

Telemedicine was utilized across the nation by health care providers and patients to minimize the spread of the COVID-19 pandemic. Below are some examples highlighting the benefits and, in some cases, challenges of using telemedicine by patients with cancer:

45% vs 34%	Forty-five percent of **patients with cancer preferred a telemedicine visit** compared to 34 percent who selected an office visit (471).
42% and 37%	Forty-two percent of **patients with cancer noted reduced travel time**, and 37 percent listed reduced risk of COVID-19 infection, as their reason for satisfaction with telemedicine (472).
87% vs 72%	Eighty-seven percent of **patients with cancer**, born between 1981 and 1995, had **higher satisfaction with access to telemedicine** compared to 72 percent of those born between 1928 and 1945 (473).
80% and 96%	Eighty percent of patients had their first telemedicine appointment for genetic services, and 96 percent of patients, including those with hereditary cancers, felt they received **quality genetic counseling via telehealth** (474).
34% vs 51%	Only 34 percent of **Hispanic patients with cancer used video-based telehealth visits** in April 2020 compared to 51 percent of Asian patients with cancer (475).
54% vs 38%	Fifty-four percent of **non-Hispanic white patients with cancer used video-based telehealth visits** from March to December 2020 compared to 38 percent of Black patients with cancer (476).

prostate cancer survivors and their spouses increased from 81 percent in-person attendance to 91 percent participation when delivered online, while the retention increased from 84 percent in person to 92 percent online. Similar results were also evident among breast cancer survivors (477). Rapid telemedicine adoption during the COVID-19 pandemic has allowed researchers to study the effects of reduced, changed, or eliminated aspects of clinical practice and patient care. For example, one study found that reduction in frequency of follow-up visits with health care providers had no adverse effect on quality of life of breast cancer survivors; instead, it improved cost-effectiveness (478).

There was a **154 percent increase in telehealth visits** during the first week of April 2020 compared to the same week in 2019 (479).

Researchers are also working to address whether a broad implementation of telemedicine will reduce or increase physician burnout, which is defined as a long-term stress reaction marked by emotional exhaustion, depersonalization, and a lack of sense of personal accomplishment (480). A 2019 National Academy of Medicine report has found that nearly half of the physicians and nurses in the U.S. have experienced symptoms of burnout (481). Telemedicine has the potential to reduce burnout among health care workers. In a recent survey evaluating physician perceptions and attitudes toward telemedicine during the pandemic, 42 percent of the respondents preferred using telemedicine over in-person visits when possible, and 36 percent reported improved work-life balance because of using telemedicine (482). Many hospitals and health systems are using telemedicine to improve work environment, provide health care workers access to mental health counselors, and facilitate better patient care (483,484).

Telemedicine permits a decentralized approach to patient care that can be paradigm shifting in delivering quality care (see **Improving**

Clinical Trial Design and Conduct, p. 72), while reducing the physical, psychological, and financial stress for patients with cancer. However, several limitations remain in realizing the true potential of telemedicine in oncology, such as lack of infrastructure, inadequate reimbursement models, insufficient community-based resources to provide in-home interventions when needed, and concerns about the privacy and protection of patient health records. Because of these limitations, full scale deployment of telemedicine can potentially widen the existing cancer health disparities by causing a "digital divide," especially for patients with limited or no access to digital communication tools. It is important to assess in depth the quantifiable impact of telemedicine on long-term clinical outcomes and patient experience, as well as to systematically identify the areas that need improving (485,486).

IMPROVING CLINICAL TRIAL DESIGN AND CONDUCT

Since the onset of the pandemic, there have been concerns that clinical studies will be adversely affected, thus hampering progress against cancer. The largest impact on clinical research was between March and May 2020 (336). Trial enrollments fell at many institutions because prospective participants reduced, or altogether stopped, hospital trips, and research staff focused their efforts on responding to the public health emergency caused by the pandemic. Some trials were terminated because they were deemed too dangerous to continue (see **Impact on Discovery Science and Clinical Studies**, p. 57). FDA and NCI quickly issued guidance during 2020 to minimize the adverse effects of the pandemic on the conduct of cancer clinical trials, offering a roadmap to streamline future cancer clinical trials, increase participation from diverse groups, and accelerate the pace of progress against cancer (see sidebar on **Lessons from COVID-19 to Streamline Cancer Clinical Trials**, p. 73).

The COVID-19 pandemic has had a transformational impact on how multiple aspects of clinical care are delivered to patients with cancer. For example, implementation of telemedicine has taken center stage in cancer care and has shown a high rate of adoption and satisfaction among patients and health care providers alike (see **Implementing Telemedicine**, p. 69). According to one survey of 245 clinical trial investigators, telemedicine-based interactions between investigators of cancer clinical trials and their patients, which was more than six times higher during the peak of the pandemic compared to the prepandemic time, remained three times higher compared to prepandemic level, even six months after the peak of the pandemic (487). The study also found that more than 75 percent of investigators who responded to the survey expected adoption of telemedicine consultation and remote patient monitoring to continue once the pandemic has completely subsided; a significant number of investigators also expected many other adaptations/modifications to clinical trials to become a regular component of clinical trials postpandemic, such as in-home nurse visits (44 percent of respondents) and supply of experimental therapeutics directly from sponsor (40 percent of respondents) or site (39 percent of respondents) of clinical trial to patient (487). Another survey found that investigators of cancer clinical trials increasingly used, or are planning to use, telemedicine (82 percent of survey respondents) and alternative locations for patient monitoring and assessment (73 percent of survey respondents) during the pandemic (376). A potential reason for such a high rate of satisfaction with telemedicine among patients and optimism among clinical trial investigators is that telemedicine can help alleviate the uniquely high burden that cancer clinical trials place on patients, e.g., on-site follow-up surveys, which can pose a barrier for patients who live far from the study site (488).

Clinical studies are expensive. According to a 2018 U.S. Department of Health and Human Services analysis of clinical trials conducted from 2004 to 2012, the cost of a phase III clinical study was more than 50 million U.S. dollars, and the three main reasons for the high cost included clinical procedures (15 to 22 percent), administrative staff compensation (11 to 29 percent), and site monitoring (nine to 14 percent) (489). A 2021 survey of different organizations involved in conducting clinical trials found that most respondents expected the cost of decentralized clinical trials to be lower than traditional clinical trials (490). Decentralized clinical trials also have the potential to increase quality of care and survival outcomes with remote monitoring tools. For example, findings from a study comparing web-based symptom monitoring in patients with lung cancer with standard follow-up show that remote symptom monitoring increased 2-year overall survival by seven months (491).

Key lessons learned from the pandemic, together with the guidance that NCI and FDA issued during the COVID-19 pandemic, highlight the opportunity to decentralize clinical trial design, so that lifesaving anticancer therapeutics can be brought quickly to as many patients as possible, without compromising the safety and efficacy of the treatments (**Figure 8**, p. 74).

The concept of decentralized or virtual clinical trials is not new (493). In fact, 33 percent of respondents to a survey of institutions that perform clinical trials indicated that they were conducting virtual trials prior to the COVID-19 pandemic (494). As we look forward to using the lessons learned from the COVID-19 pandemic to modernize cancer clinical trials, some challenges remain. A key consideration for virtual clinical trials will be to ensure secure and safe sharing and exchange of electronic health records containing sensitive patient data. Educating both patients and the clinical research staff to use the digital tools necessary to implement a decentralized clinical trial, as well as to accurately report data in a timely manner, will also require financial and technical resources as well as time and training. It will be equally important to ensure that a decentralized trial for a specific anticancer drug is feasible and safe for the participants (for example, it may be easier to conduct a decentralized clinical trial for a drug that can be taken orally and thus can be delivered to patients at home compared to a therapeutic that requires intravenous infusion at the clinic).

It is well established that the clinical trial participation of racial and ethnic minorities and other medically underserved populations remains low; the FDA 2021 summary report on the diversity of clinical trial participants showed only eight percent Black and 11 percent Hispanic participation in clinical trials for the drugs approved in 2020 (495). Therefore, it is concerning, albeit unsurprising, that the use of telemedicine, a major conduit for decentralized trials, during the pandemic has been significantly lower among patients from racial and ethnic minorities and other medically underserved populations (496-498).

The potential of decentralized trials to reduce time and cost of traveling to clinical trial centers offers an opportunity to

LESSONS FROM COVID-19 TO STREAMLINE CANCER CLINICAL TRIALS

The guidance issued by FDA and NCI during 2020 to minimize the adverse effects of the pandemic on the conduct of cancer clinical trials offers valuable lessons that can be implemented to streamline future cancer clinical trials, increase participation from diverse groups, and accelerate the pace of progress against cancer. These lessons include:

Consenting remotely using electronic means to participate in a clinical trial.

Currently, in-person consent is required to participate in a cancer clinical trial.

Allowing the use of any laboratory and imaging centers that meet the specifications required for participation in a clinical trial.

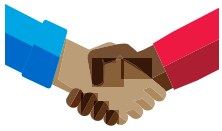
Currently, individuals are required to use a clinical trial-specified laboratory or imaging center.

Permitting telehealth approaches for routine clinical assessments, such as safety of the experimental treatment.

Currently, individuals are required to visit clinics in person for these evaluations.

Increasing the engagement of community-based network sites in conducting a clinical trial.

Currently, experimental therapeutics are only available at the institutions where clinical trials are being conducted.



Delivering experimental drugs directly to patients.

Currently, an in-person visit is required to receive experimental drugs.

Making clinical trials more accessible to underserved populations and those living in rural areas.

Currently, underserved populations have limited access to clinical trials for a variety of reasons.

Adapted from (38).

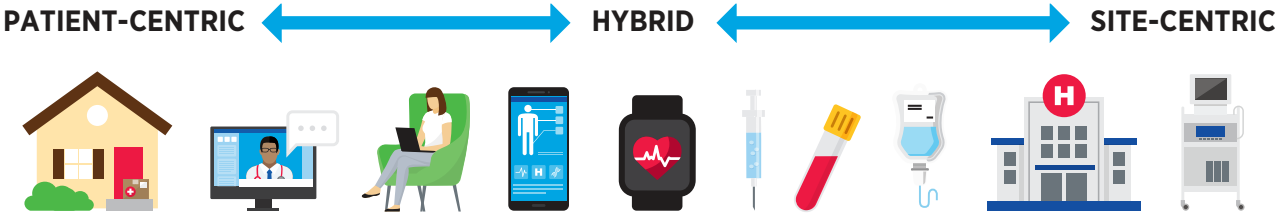
increase participation of racial and ethnic minorities and other medically underserved populations in clinical trials. However, realizing an equitable decentralized clinical trial design for all patients, regardless of age, gender, race, ethnicity, socioeconomic status, and/or geographic location, will require modernizing infrastructure that includes universal access to high-speed Internet through broadband connection and/or Wi-Fi hotspots, and the development of digital tools that are easy for all patients to use. Such approaches will help minimize the emerging impact of virtual cancer clinical trials on widening cancer health disparities, especially those based on age and socioeconomic status (see **Impact on Cancer Health Disparities**, p. 67) (492).

RETHINKING CANCER TREATMENTS

The COVID-19 pandemic has affected how clinical oncologists and cancer researchers approach cancer treatments. For example, preventive measures to contain the spread of COVID-19 resulted in interruptions or delays in certain cancer treatments, such as surgery or chemotherapeutic infusions, that require visiting a health care facility because of the complexities associated with their delivery. Moreover, certain treatments, such as chemotherapy, which are a part of routine cancer care, result in weakened immune systems, making those being actively treated for their cancer more vulnerable to COVID-19 infection (see sidebar on **Why Are Cancer Patients at an Increased Risk of Infection?**, p. 44).

During the early months of the pandemic, FDA used data from initial phase III cancer clinical trials to approve a revised dosing schedule for pembrolizumab (Keytruda), a commonly used immune checkpoint inhibitor to treat advanced lung cancer and many other cancer types (38), from 200 mg every three weeks to 400 mg every six weeks (499,500). These measures helped reduce recurrent hospital visits, which have been identified as potential risk factors for infection with SARS-CoV-2 (501,502). Other potential advantages of redosing strategies for immune checkpoint inhibitors may include reduced side effects as well

FIGURE 8 DECENTRALIZING THE CLINICAL TRIAL DESIGN: BRINGING CARE TO THE PATIENT



Depicted here are the key elements of fully centralized and decentralized clinical trials. The traditional clinical trial design engenders a high degree of process control, such as research sites that are fully capable of handling complex procedures associated with clinical trials. However, the trade-off has been high cost for clinical trials and low patient accrual. Decentralized or virtual trials are built around the concept that some elements of a clinical trial can be safely and reproducibly performed in a patient's home or at a local physician's office via digital health tools. Because cancer clinical trials are often complex, requiring skilled staff to treat and monitor patients on a regular basis, a hybrid model for clinical trials to test new anticancer treatments will likely yield the most benefit for patients with cancer.

Modified from (492).

as decreased financial burden for patients. However, long-term studies are needed to identify any adverse effects of the revised dosing of these lifesaving anticancer treatments on clinical outcomes for patients with cancer.

Patients with cancer expressed anxiety and concern about missing cancer treatment early during the pandemic and its potential impact on their overall health (see **Impact on Cancer Treatment**, p. 63). To alleviate these concerns and to develop scientific evidence on whether a delay in cancer treatment during the pandemic will have an adverse impact on patients with cancer, researchers analyzed data from patients with cancer from the National Cancer Data Base that encompasses more than 70 percent of new cancer diagnoses in the U.S. (503). One study examined data between 2010 and 2016 and investigated whether patients with certain types of noninvasive and invasive early-stage breast cancer experienced any negative impacts, such as cancer diagnosis at a more advanced stage or a decrease in overall survival, because of delays in surgery. The usual treatment for this type of cancer is surgery soon after diagnosis. Researchers found that greater than 98 percent of the patients underwent surgical treatment within 120 days of diagnosis, and that this longer wait was not associated with diagnosis of a more advanced-stage cancer later. Even in patients who had a slightly greater risk of developing advanced-stage cancer because of the delay in surgery, there was no negative impact on overall survival (504). The second study analyzed data from 2004 to 2014 and found that up to a 6-month delay in treatment of patients with intermediate-, high-, or very high-risk prostate cancer with radiation was not associated with worse overall survival (505). Consistent with these findings, studies have found little to no evidence that delayed or modified cancer treatments because of the pandemic have adverse outcomes for patients with cancer (506).

It is, however, important to note that the outcome of delayed treatment likely depends on the type and stage of cancer. For example, one study found that patients with colon cancer had an increased 5-year predicted mortality if time-to-treatment was delayed from 61-120 days (39 percent) to 181-365 days (48 percent) (507). Delayed anticancer treatment can also increase the likelihood of disease recurrence, as has been reported for patients with stage I non–small cell lung cancer; for each month of surgical delay beyond 12 weeks, the risk of disease recurrence for these patients increased by 1.6 percent (508). These findings point to the importance of patients with cancer consulting with their health care providers about the risks and benefits of delaying treatment of cancer. Furthermore, these findings also underscore the opportunity to develop scientific evidence and consensus for re-evaluating current treatment regimens in a manner that leads to better clinical outcomes for patients with cancer.

ACCELERATING COLLABORATIONS, RESOURCE SHARING, AND TEAM SCIENCE

Progress against cancer is driven by a collaborative and team science approach to cancer research. Years-long interdisciplinary collaborations among key stakeholders have resulted in major discovery science milestones, leading to lifesaving clinical breakthroughs. But the speed and scale of achievement during the COVID-19 pandemic—globally, 25 vaccines have been approved as of January 1, 2022, with many additional vaccines in various phase III clinical trials—are rare, if not unprecedented (509). According to a report from the Organization of Economic

Co-operation and Development (OCED), an international organization with 38 member countries, including the U.S., around 75,000 scientific papers on COVID-19 were published from January to November 2020, with the highest level of collaboration between scientists in the U.S. and China; three quarters of the papers were open access and freely available to other researchers (510). Moving forward, it will be pivotal for stakeholders in academia and the biopharmaceutical industry to devise open communication channels for sharing critical data necessary for developing effective therapeutics while preserving the intellectual property rights of all involved.

> **"Pandemic definitely delayed and slowed my research activities, progress and negatively impacted funding opportunities. On positive side, as resources were limited, it encouraged me to think more innovatively, collaborate better and be time efficient."**
>
> **Preshita Desai, PhD**
> **Research Scientist, Western University of Health Sciences, Pomona, California**
> 2019 AACR-Novocure Tumor Treating Fields Research Fellowship Recipient

Nowhere has the collaborative and team science spirit been more apparent than in the unprecedented speed with which vaccines against COVID-19 were developed. The traditional pathway to developing a vaccine or an anticancer drug, from target discovery and validation to bringing it to the clinic, can take up to 10-15 years (511,512). On April 17, 2020, the NIH announced a public-private partnership—Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)—to develop a coordinated research strategy for prioritizing and accelerating the development of the most promising vaccines and therapeutics against COVID-19. ACTIV brought together the NIH and other U.S. government agencies; the European Medicines Agency (EMA); and representatives from academia, philanthropic organizations, and numerous biopharmaceutical companies (164). Similarly, the National Institute of Allergy & Infectious Diseases (NIAID) founded a new clinical trial network, the COVID-19 Prevention Trials Network (COVPN), to leverage existing infrastructure and engage communities to facilitate the enrollment of the thousands of volunteers needed for late-stage clinical trials of promising vaccines against SARS-CoV-2.

Vaccine development for COVID-19 provides a blueprint for the rapid development of vaccines and other therapeutics against deadly diseases, including cancer types for which there are not many treatment options available (513).

POLICIES TO COMBAT THE IMPACT OF A GLOBAL HEALTH CRISIS ON CANCER SCIENCE AND MEDICINE

In this section, you will learn:

- How supplemental research funding for NIH would help restore momentum against cancer.
- How FDA's efforts to encourage changes in the conduct of cancer clinical trials are making them more patient centered.
- How expanding telehealth increases access to cancer care for patients during COVID-19.
- How disruptions to cancer research and society during future pandemics could be minimized by learning from COVID-19 and increasing the cancer community's resilience.
- How building confidence in public health and combating misinformation protects patients with cancer by increasing vaccinations and promoting evidence-based cancer control and treatment options.

The COVID-19 pandemic challenged the medical research community in many ways, including through the loss of productivity because of the suspension of laboratory activities and delays in reporting results of ongoing basic and clinical research (see **Impact on Research Funding and Workforce**, p. 56). These issues came at a substantial cost to the medical research community. The former NIH Director, Francis S. Collins, MD, PhD, estimated that NIH and its grantees lost approximately $16 billion in research costs (514).

STEPS THAT HELPED OFFSET THE PANDEMIC'S IMPACT ON CANCER RESEARCH

NIH took many important steps to assist researchers during these challenging times, including extending deadlines for applications, allowing delayed submission of preliminary data after grant deadlines, authorizing grants to cover salaries and stipends of scientists during laboratory closures, and extending project timelines and requirements. In targeting assistance to early-career researchers, NIH also extended eligibility periods for early-stage investigators and trainees and permitted the carryover for institutional training grants if they had been previously approved (515,516).

NIH and NCI also provided flexibility with timelines and funding, such as no-cost extensions, case-by-case administrative supplements for unanticipated costs, and funded extensions on some grants due to delays caused by COVID-19. Additionally, NIH fellowship ("F") and career development ("K") award recipients were allowed to request a funded extension if their training or career development had been "significantly hindered over and above lost research productivity that most individuals experienced because of COVID-19 related shutdowns" (517).

> **"I urge Congress to provide additional funding opportunities for research fellows and early-stage investigators. These individuals were disproportionately impacted by COVID-19. It will permanently damage our scientific pipeline if we do not recognize and work to alleviate this issue."**
>
> **Jessica E.S. Shay, MD, PhD**
> **Postdoctoral Fellow, Koch Institute for Integrative Cancer Research, Cambridge, Massachusetts**
> 2021 Bosarge Family Foundation-Waun Ki Hong Scholar Award for Regenerative Cancer Medicine Recipient

As noted in **The AACR Call to Action** (p. 83), significant funding is needed to defray these costs and solidify the medical research enterprise. The broader medical research community, including AACR, continues to advocate for NIH to receive emergency supplemental funding to offset the costs caused by the pandemic and support the medical research workforce (518).

PANDEMIC-RELATED FLEXIBILITIES FOR CANCER CLINICAL TRIALS

The COVID-19 pandemic greatly impacted the conduct of cancer clinical trials by exacerbating existing hurdles for trial participation. In response, FDA outlined voluntary flexibilities

for clinical trials in March 2020 (see **Improving Clinical Trial Design and Conduct**, p. 72) (519), including:

- Using telemedicine to assess outcomes and wellness;
- Home delivery of trial medications;
- Remote consenting; and
- Collaborations with local clinics, imaging facilities, and laboratories.

FDA has recommended these modifications to cancer clinical trials in the past, but the COVID-19 pandemic greatly increased their acceptance among trial sponsors. If implemented permanently, these changes could decrease costs and make it easier for patients with cancer to participate in trials.

In collaboration with NCI and other stakeholders, FDA is researching which flexibilities and adaptations are the most important to keep permanently (520). One key strategy will be to add lines of investigation to postapproval therapeutic trials to test differences in protocols and the types of data collected, such as patient-reported outcomes (521). Additionally, the NCI Cancer Therapy Evaluation Program is currently conducting retrospective analyses of trials that were active before and during the COVID-19 pandemic to determine how changes impacted recruitment and data quality (521). NCI has also issued administrative supplements for institutional P30 clinical research grants to assess the feasibility of integrating trial forms directly into electronic health records systems (522). It is important to note that regulatory decisions like these do not happen in a vacuum. FDA and NCI will seek input from all stakeholders, including patient advocates, informally and formally at events such as workshops and major scientific conferences.

Increasing the representation of racial and ethnic minorities and other medically underserved populations in cancer clinical trials has also been a key priority of FDA during the pandemic. In early 2020, the FDA Oncology Center of Excellence launched Project Equity to improve the evidence base for underrepresented populations in trials by issuing guidance to facilitate recruitment of diverse patients, stakeholder collaboration, and analysis of outcomes (523). Additionally, the FDA Center for Drug Evaluation and Research and the Center for Biologic Evaluation and Research issued voluntary guidelines in November 2020 that would increase representation of racial and ethnic minorities (524), including:

- Expanding eligibility criteria for large efficacy trials;
- Implementing strategies to improve recruitment of participants who reflect the diversity of the patient population;
- Encouraging trial sponsors to definitively determine the safety and efficacy of investigational therapies in racial and ethnic minorities through sufficient recruitment or follow-up studies;
- Maintaining data quality and patient safety while partnering with local health facilities in decentralized trials; and
- Leveraging real-world evidence to fill gaps in evidence where the feasibility of randomized clinical trials may be limited.

As noted in **The AACR Call to Action** (p. 83), Congress should support FDA's initiatives to improve the drug development and review process by increasing the discretionary budget authority by at least $343 million in FY 2022. Additionally, Congress could support efforts to increase diversity in clinical trials by passing the Diversifying Investigations Via Equitable Research Studies for Everyone (DIVERSE) Trials Act.

The **DIVERSE Trials Act** (H.R. 5030/S. 2706) would **require the U.S. Department of Health and Human Services (HHS) to issue guidance on decentralizing clinical trials**, allow sponsors to provide free digital devices to bridge gaps in technology access, and permit HHS to offer grants to support education, outreach, and clinical trial recruitment.

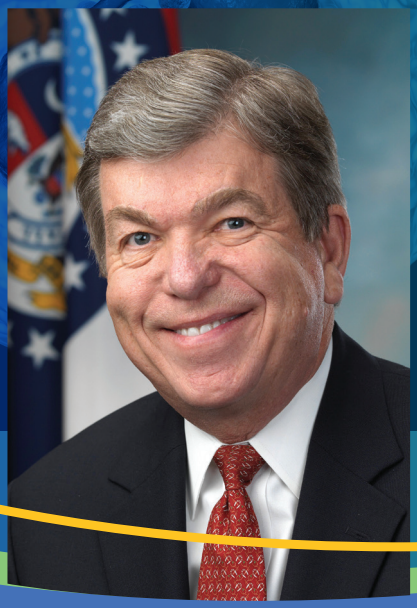
LESSONS FOR PRIORITY VACCINATION OF PATIENTS WITH COMPROMISED IMMUNE SYSTEMS, INCLUDING PATIENTS WITH CANCER

One of the most valuable lessons learned from COVID-19 was how to rapidly develop safe and effective vaccines. The novel mRNA vaccine technology, originally developed to treat cancer, enabled early phase clinical trials to start within two months after the genomic sequence of SARS-CoV-2 was published (131).

As detailed in prior sections (see **Varied Responses to COVID-19 Vaccines in Patients with Cancer**, p. 47), unvaccinated patients with cancer are twice as likely to die from COVID-19 compared to unvaccinated patients without cancer (204). Because of the increased risk, AACR and 140 other cancer-focused organizations advocated for patients with cancer, survivors of cancer, and their caregivers to be prioritized for vaccinations (525). Indeed, many states and countries prioritized patients with cancer and others with elevated risk of severe COVID-19 disease for vaccination, although prioritization orders varied greatly (526,527). However, many of these patients prioritized for vaccination were excluded, or were not adequately represented, or their data were not stratified in large vaccine efficacy trials (528,529).

Of the three vaccines authorized in the United States, only the Johnson & Johnson vaccine phase III trial specified the number of patients with cancer or survivors of cancer included in their trial (530). It is critical that vaccine trials in a future pandemic include adequate numbers of patients with cancer to inform their clinical use in this key patient population. Furthermore, additional studies have found that patients with cancer may also receive more benefit than the general population from a third vaccine dose (285,291). Therefore, AACR also advocated for the Biden administration to recommend three doses for patients with cancer and survivors of cancer and booster doses for caregivers and household members of patients with cancer (282).

Continued on page 79



THE HONORABLE ROY BLUNT
Age: 72 | U.S. Senator for Missouri

Investing in Innovation to Respond to COVID-19 and Continue Progress Against Cancer

There is no question we are at an exciting moment for health research. In less than one year, the federal government developed several vaccines, therapeutics, and diagnostic tests to respond to the COVID-19 pandemic. During shutdowns and social distancing, our research infrastructure was tested like never before, and it prevailed.

Our success in quickly and safely developing vaccines and other tools to fight the virus is due to years of investment in the National Institutes of Health (NIH). Our accomplishments didn't begin when the virus was discovered; they began decades earlier, out of the spotlight, with investments in basic research.

As the top Republican on the Senate appropriations subcommittee that funds health care programs, I've been proud to work with my colleagues to increase NIH research funding by nearly 43% in the past six years. This was after a decade of stagnant funding. Last year, our subcommittee provided an additional $4.8 billion to NIH for COVID "long-haulers" research, diagnostic test development, and research on how the virus spreads and mutates. This has proven critical to some of our most fundamental knowledge about COVID-19, including its impact on high-risk people like those with cancer and cancer survivors. Early NIH-supported research showed that patients with cancer were at greater risk for severe illness, which helped shape important public health recommendations.

Through the five bipartisan COVID-19 relief bills passed last year, the subcommittee provided more than $320 billion to the Department of Health and Human Services (HHS) to combat the virus. This included funding for medical research, for Operation Warp Speed to develop and deploy vaccines and therapeutics, and for the acceleration of diagnostic testing efforts. One of our nation's great successes during the pandemic was our ability to develop tests, treatments, and vaccines rapidly. It happened because the federal government became a more active partner in research and development instead of just a sponsor.

At the height of the pandemic, when diagnostic tests were in short supply, former Senator Lamar Alexander and I created NIH's RADx program to fast-track more tests to market using a "Shark Tank"-style process. From 716 ideas, there were 32 diagnostic tests developed and commercialized, increasing availability of tests across the country by more than two million per day. Through Operation Warp Speed, HHS was able to narrow approximately 100 COVID-19 vaccine candidates to the top six and simultaneously provide funding for their research, development, and manufacturing. As a result, when a vaccine earned approval, it was ready to be distributed immediately.

This model may be the most important concept to emerge from the pandemic, demonstrating that active collaboration between the federal government and the private sector, coupled with significant funding, can create scientific breakthroughs—potentially in record time. It also raises the possibility of replication. What if we could do for cancer or Alzheimer's disease or ALS what we did for COVID-19?

Two COVID-19 vaccines proved the mRNA platform could be used for vaccine development. Why has it not worked for a cancer vaccine after decades of research? Researchers have already developed blood tests to detect several types of cancer, but they're still not in wide use. What if the federal government replicated the COVID-19 research model for a cancer vaccine or diagnostic test? What if the government took more targeted financial risks and became a real partner, like a venture capitalist, in the research for cancer? Why shouldn't we?

If there is one lesson we must take from this pandemic, it is that our nation's success depends on the medical research infrastructure supported by the NIH. Our COVID-19 research and development efforts have transformed how we fund science. They have shown that we can find solutions in times of crisis at extraordinary speed. Now is the time to build upon that success.

TELEHEALTH POLICIES DURING COVID-19 AND THE IMPACT ON THE CANCER CARE CONTINUUM

The federally declared public health emergency in response to the COVID-19 pandemic resulted in unprecedented, rapid shifts to support flexible telehealth use for both health care providers and the patients they serve (see **Implementing Telemedicine**, p. 69). For patients with cancer and survivors of cancer, the temporary changes to telehealth coverage provided by Congress or implemented by CMS address overlapping areas across the cancer care continuum.

Among the most significant changes for health care delivery were CMS's provision of an expanded use of telehealth for more than 80 additional services for seniors covered by Medicare and CMS's approval of telehealth for state-run Medicaid and CHIP health insurance programs (531). In April 2020, CMS created a toolkit for states to accelerate adoption of telehealth coverage policies for Medicaid and CHIP (532). By providing reimbursement for many telehealth services, CMS opened the door for patients to consult with their physicians without having to risk their health by entering a medical facility.

The Coronavirus Aid, Relief, and Economic Security (CARES) Act, enacted in March 2020, provided $2.2 trillion in economic stimulus, emergency support for hospitals and health care providers, investments in COVID-19 testing, vaccines, and therapeutics, as well as provisions to expand coverage for telehealth. Specifically, the temporary expansion of the Medicare and Medicaid telehealth services benefit under the 1135 waiver authority in the CARES Act removes previous geographic constraints associated with telehealth use and reimbursement (533). Providers are allowed to: expand telehealth delivery to patients in every part of the country; permit health care providers to practice across state lines if permissible by the state; serve new and established patients; and supervise patients using either audio or video communication. The four main types of virtual services covered under Medicare include telehealth visits, virtual check-ins, e-visits, and audio only. Although these flexibilities have been implemented and some are slated to continue through 2023 (534), adverse differences in technology access, digital literacy, and infrastructure to support these efforts disproportionately impact chronically disadvantaged groups (535,536).

> **"Cancer is a major problem with increasing social and economic consequences. COVID-19 has masked this impact. Increased resources for cancer research is needed so loved ones in the future can have improved therapeutics and outcomes."**
>
> **Albert Kim, MD**
> **Neuro-Oncologist at MGH Cancer Center**
> **Instructor in Neurology, Harvard Medical School**
> 2021 AACR-Pfizer Breast Cancer Research Fellowship Recipient

Health care delivery and improved patient outcomes are additionally supported by the use of electronic health record (EHR) systems. The Health Information Technology for Economic and Clinical Health (HITECH) Act was enacted as part of the American Recovery and Reinvestment Act of 2009. Health care providers were encouraged to securely use electronic health records and improve security protections for health data sharing (537). A temporary, COVID-19 related amendment to the HITECH Act in January 2021 focused on regulatory requirements and Health Insurance Portability and Accountability Act of 1996 (HIPAA) violation enforcement; however, requiring the effective use of EHR systems to capture appropriate health-related data, safeguarding health information sharing, and mandating public health reporting could support patients with cancer in this and future pandemics (538,539). Amended provisions in HIPAA also allowed covered health care providers to deliver telehealth through popular, non-public-facing video chat and text-based applications without the risk of penalty (533). Secure and timely health data sharing between providers has the potential to improve outcomes for patients with cancer during and after the COVID-19 pandemic.

POLICIES TO ADDRESS DISPARITIES EXACERBATED BY THE PANDEMIC

The social determinants of health (SDOH) are defined as the conditions in which people are born, live, learn, work, play, worship, and age that affect their health and quality of life (540). The five domains of SDOH include economic stability, education access and quality, health care access and quality, neighborhood and built environment, and social community context. Policies described previously (see **Telehealth Policies During COVID-19 and the Impact on the Cancer Care Continuum**, p. 79) have the potential to improve one of the SDOH domains: health care access and quality. The CARES Act helped offset unexpected clinical costs associated with the response to COVID-19 for providers, and the HITECH amendments encouraged the safe and efficient use of health data between health care providers. For patients with cancer, it is imperative to consider the entire SDOH framework in the context of the cancer care continuum as policies are designed and implemented to combat the ravages of the COVID-19 pandemic (See **The AACR Call to Action**, p. 83).

LESSONS FOR INCREASING HEALTH CARE ACCESS AND INSURANCE COVERAGE

One of the most important factors associated with quality cancer care and survival is insurance coverage (65,541). The COVID-19 pandemic contributed to fluctuations in employer-sponsored health insurance and Medicaid enrollment (542), thus disrupting health care access and quality. This is alarming as disruptions in insurance have the potential to increase the risk for adverse outcomes for patients with cancer. Reported disparities in cancer screening, stage at diagnosis, and mortality rates for those who are uninsured are described in greater detail in the *AACR Cancer Disparities Progress Report 2020* (65).

Continued on page 81

THE HONORABLE AMY KLOBUCHAR
Age: 61 | U.S. Senator for Minnesota

Advocating for Cancer Research and Early Detection from Personal Experience

I would like first of all to thank the researchers at the American Association for Cancer Research who contributed to this special report on COVID-19 and cancer. As we continue our efforts to detect disease early, improve treatment practices, and ultimately find new cures and vaccines for cancer, this research is critical.
I also want to recognize all of the doctors, nurses, and other health care personnel who are working every day on the front lines caring for patients with a coronavirus infection or cancer. I recently visited the emergency room in our biggest public hospital in Minneapolis and it really hit home to me that this isn't over by any means. Even though so many people have now been vaccinated and we continue to find new and exciting treatments, it's been an exhausting and difficult year, so I thank you all for your extraordinary work.

The topic of cancer and early detection is personal for me. Following a routine mammogram last February, I learned that I had stage IA breast cancer. Thanks to my incredible doctors and nurses, the treatment went well, and my doctors believe that my chances of developing cancer again are no greater than those of the average person. Those aren't the stories that you used to hear—that cancer was caught so early that you could get through it with a lumpectomy and radiation. As often happens for anyone dealing with an illness, this experience gave me time to reflect on my own life and those I love. It was a reminder that each day is a gift.

I shared my story to call attention to the fact that because of the pandemic, many people have been delaying physicals and routine exams, including the kinds of tests that can help people catch cancer early. I know that because I delayed mine. I've heard from so many people across the country since that day. I've had people text me or write on Twitter that they're in the waiting room right now to get their mammogram or their colonoscopy. That's kind of a fulfilling thing, but there are still thousands of people walking around with undetected cancer because they're not going in to get that preventative care. With many Americans behind on their regular checkups, we need to do more to make sure they have the resources and information they need to access this potentially lifesaving care. That's why I introduced the bipartisan Preventative Care Awareness Act with Senators Susan Collins and Mike Rounds—who, tragically, recently lost his own wife, the love of his life, to cancer—to promote screenings and create a public health task force to encourage preventative care and address disparities in these services. I'm going to keep fighting until we get this done.

But prevention is just one part. We also have to invest in medical research so that we can develop new treatments and cures for cancer and respond to any future pandemics. I recently fought to increase funding for the National Institutes of Health and I will continue to push for more permanent, stable resources so we can make the next great discovery. I was honored to be there when President Obama and now President Biden signed the Cancer Moonshot into law, and I want to be there for the next great discoveries and all the work that comes straight from you on the front lines. We can find new solutions, new treatments, and new cures, and save lives.

Before I close, I have a message for anyone living with cancer. I know you're in a big fight right now. But you're not in it alone. I'm in your corner, sending you strength and love. And I know the entire AACR community is doing the same.

So, keep up the amazing work. I'm proud to be your partner, and I'm going to be with you every step of the way. You know what a difference that makes, because you do it for other people all the time. Thank you.

BUILDING RESILIENCE FOR A FUTURE PANDEMIC

To minimize interruptions to cancer science and medicine during a future pandemic, it will be extremely important to address an emerging pathogen before it spreads widely in the community. Sustained and predictable public health funding is vital to build the infrastructure, reporting systems, and workforce before a pandemic or other health crisis starts. Unfortunately, public health and pandemic preparedness programs have suffered from slow funding growth or funding cuts between emergencies, and supplemental funding is then needed when an emerging threat becomes a crisis (543-546). For example, the U.S. Department of Health and Human Services' (HHS) Hospital Preparedness Program, designed to prepare health care facilities for a wide variety of health crises, decreased from $515 million in FY 2004 to $276 million in FY 2020 (544). In total, the federal COVID-19 relief packages provided approximately $400 billion in emergency funding to directly help federal agencies, states, cities, tribes, and health facilities fight the pandemic (547). While beneficial for addressing this crisis, had the public health infrastructure and surveillance been stronger before 2020, there could have been a more swift and secure response that avoided disruptions to cancer research, health care, and the broader society. Robust and sustainable investments in public health will be needed to rebuild the public health infrastructure and workforce and have them emerge stronger before a future public health emergency (544).

COLLECTING HIGH-QUALITY PUBLIC HEALTH DATA

Effective pandemic responses and cancer control efforts rely on timely and high-quality data. However, public health reporting systems in the United States and the types of data collected vary greatly and lack coordination (548-551). Many states still rely on fax machines and spreadsheets that are manually re-entered into federal computer systems, which increase the risk of human error (552). For these reasons, AACR urged President Donald J. Trump and Congress in the spring of 2020 to establish a de-identified nationwide public health reporting system (553,554). In FY 2020 and FY 2021, Congress appropriated $50 million for CDC Data Modernization activities (555), and an additional $1 billion was included in the CARES Act and the American Rescue Plan. These funds are a down payment on a modern public health reporting system that could greatly increase the speed and quality of data for future pandemics as well as chronic disease initiatives.

TESTING AND TRACING INFECTIONS EFFECTIVELY

Stopping a pandemic pathogen before it has a chance to establish itself within a community requires an effective testing, tracing, and isolation program, which has been the cornerstone of pandemic responses for decades (556-558). Unfortunately, asymptomatic transmission, reliance on a single flawed test, and political interference with the CDC response caught the United States off guard early in the COVID-19 pandemic (550,559-561). Fortunately, by the summer of 2020, NIH's RADx initiative along with state, academic, and private laboratories facilitated a spectacular ramp-up of testing, demonstrating the power of public-private partnerships in emergency responses (562-564). A robust public health workforce and earlier activation of this efficient test development model in a future pandemic could greatly improve early testing and tracing efforts. Additionally, ensuring that contagious and potentially contagious individuals take necessary precautionary measures is crucial for limiting further spread of a pathogen. It is especially important for those who may come into contact with patients with cancer, including health care workers, to stay home and isolate if they are exposed or contagious.

SUPPORTING A ROBUST HEALTH CARE WORKFORCE

The pandemic has also exacerbated critical shortages of health care providers, including those who care for patients with cancer. Prior to the pandemic, there was an estimated shortage of more than 150,000 nurses and 30,000 physicians in the United States, which contributed to delays in cancer care and provider burnout, and decreased the quality of care (518,565,566). Since the onset of the pandemic through September 2021, 30 percent of health care workers have either quit their jobs or were laid off, including 534,000 who quit in August 2021 alone (567,568). Furthermore, the scarcity of personal protective equipment led to the deaths of more than 3,600 U.S. health care workers from COVID-19 in 2020 (569,570). These staffing shortages, especially during local surges of COVID-19, contributed to suspension of cancer-related surgeries and other delays in cancer care (571). Addressing crucial bottlenecks in the training of nurses and physicians could help alleviate long-term shortages of health care workers to care for a growing number of cancer survivors and prepare for a future pandemic (572,573).

> **"We need continued financial support that provides opportunities to innovate and security to be bold and creative."**
>
> **Gregory Beatty, MD, PhD**
> **Director of Clinical and Translational Research**
> **Penn Pancreatic Cancer Research Center**
> **Associate Professor, Medicine**
> **University of Pennsylvania, Philadelphia, Pennsylvania**
> 2020 AACR-The Mark Foundation for Cancer Research "Science of the Patient" (SOP) Grant Recipient

COMBATING MISINFORMATION AND BUILDING CONFIDENCE IN PUBLIC HEALTH

The foundation of modern medicine is the approval of therapeutics and preventive interventions based on the evidence of treating a disease with acceptable side effects. However, mistrust in the medical establishment, regulatory bodies, and private industry, as well as advances in digital communication and foreign disinformation campaigns, continues to fuel the spread of medical misinformation (see sidebar on **COVID-19 Vaccine Misinformation and How to Address It**, p. 53). Patients with cancer are especially inundated with harmful misinformation from advertisements and contacts on social

media after posting about their diagnosis (574). Addressing misinformation and building confidence in COVID-19 vaccines also help protect patients with cancer with compromised immune systems by increasing the likelihood that their families and the people they meet are vaccinated.

Additionally, lessons learned from COVID-19 vaccination campaigns could inform efforts to build confidence in HPV vaccines and promote cancer screenings. To build trust in public health, it is paramount that government agencies follow the most credible science, transparently communicate how decisions are made, and remain independent from political pressure (559,560,575-577). It is also important for scientists and medical providers to establish long-term, two-way relationships with trusted community leaders and the general population (578). In addition to building confidence in public health, these relationships can help research institutions direct their efforts toward the issues most important to the communities they serve.

THE AACR CALL TO ACTION

Decades of investment in basic, translational, and clinical research have enabled scientists to develop COVID-19 diagnostics, treatments, and vaccines at a pace never seen before, as highlighted by **Senator Roy Blunt** (see p. 78). This robust approach to medical research has saved hundreds of thousands of lives from COVID-19 in the United States and increased protection for patients with cancer who are at significant risk of developing serious cases of COVID-19.

Cancer researchers were uniquely positioned to respond to the challenges posed by COVID-19 and have played a vital role in combating the pandemic while continuing their quest to cure cancer. NCI's Frederick National Laboratory for Cancer Research, which specializes in HPV, serology, and antibody science, was able to pivot to evaluate COVID-19 antibody tests to ensure that members of the public have accurate information about the levels of their antibody response to COVID-19.

Yet the pandemic also took its toll on cancer research and prevention initiatives. The staggering delays in clinical trial activations and disruptions to ongoing trials resulted in significant financial losses and jeopardized trial outcomes. Cancer screenings are also yet to return to prepandemic levels, contributing to a likely increase in more advanced cancer diagnoses in the years ahead (432).

The pandemic also exposed the need for greater investments in public health and medical research and led to a watershed moment for modernizing how patients receive care. Under the CARES Act, CMS flexibilities to expand telehealth services are only permitted during the public health emergency. As a result, without congressional action, when the public health emergency ends, so would CMS coverage of expanded telehealth.

This Call to Action builds on what was learned during the public health emergency and lists steps that should be taken to rebuild our public health infrastructure, enhance medical research, and modernize how patients receive care and enroll in clinical trials.

INVEST IN MEDICAL RESEARCH AND THE WORKFORCE

- Offset pandemic-related research costs by providing at least $10 billion for NIH and its grantees in emergency supplemental funding as proposed in the Research Investment to Spark the Economy (RISE) Act of 2021.
- Increase investments in cancer research and prevention by supporting robust, sustained, and predictable growth for NIH and NCI, including at least $3.5 billion and $1.1 billion, respectively, in Fiscal Year 2022 for a total funding level of $46.4 billion for NIH and $7.6 billion for NCI.
- Expand tax policies to encourage philanthropic giving so that nonprofit cancer research organizations can continue to fund high-risk, high-reward research proposals and accelerate the discovery of new treatments and cures.

REBUILD PUBLIC HEALTH INFRASTRUCTURE AND STRENGTHEN PANDEMIC RESPONSE

- Develop a multiyear investment strategy to rebuild capacity of state, local, and federal public health infrastructure, including the health care workforce and the Strategic National Stockpile, so that the United States will be in a better position to combat a future pandemic.
- Empower public health officials to speak directly to the public about the science of health emergencies and invest in a comprehensive national public health data reporting system to better track public health threats and diseases, including cancer.
- Support CDC's National Center for Chronic Disease Prevention and Health Promotion to reduce the incidence of comorbid chronic conditions that increase the risk of developing cancer or severe symptoms from infectious diseases. These investments should include $559 million in FY 2022 for Cancer Prevention and Control Programs to support comprehensive cancer control, cancer registries, and screening, and devise targeted strategies for public awareness campaigns designed to encourage and build on prepandemic screening levels.

EXPAND ACCESS TO HEALTH CARE AND TELEHEALTH

- Enact policies that broaden health care coverage and reduce inequities in access to health care, such as expanding Medicaid.
- Deliver a permanent extension of CMS-approved telehealth services and support greater access to telehealth by providing funding, including grants, to support high-speed broadband, reach underserved areas, and address the digital divide.

STRENGTHEN AND MODERNIZE CLINICAL TRIAL DEVELOPMENT

- Support FDA's regulatory science initiatives and advance the development of oncology products by providing an increase of at least $343 million in discretionary budget authority in FY 2022.
- Increase diversity in clinical trials and alleviate the financial burden on prospective trial participants by reimbursing patients for ancillary trial-related costs, such as transportation and lodging, as contained in the DIVERSE Act.

The past two years have been some of the most challenging times ever faced by the United States and the entire world. Almost one million Americans have died from COVID-19 and millions more continue to suffer from long-term symptoms and major disruptions to everyday life. The pandemic also highlighted the crucial need for robust investments in medical research and the health care workforce. Cancer researchers and clinicians have been on the front lines helping develop safe and effective COVID-19 vaccines and treatments at a record pace as well as caring for severely ill patients.

In the face of the current health crisis due to the COVID-19 pandemic, cancer and other diseases continue to be major ongoing challenges. If we hope to reach the day when cancer is no longer a major health threat to our nation's citizens, Congress must provide the funding that is essential for research supported by NIH and NCI. All stakeholders must also take all necessary steps to strengthen our nation's public health infrastructure and the health care workforce so that we are better prepared for a future crisis. Robust, sustained, and predictable annual funding increases for the federal agencies dedicated to advancing public health will foster future scientific advances, maximize returns from prior investments in medical research, drive economic prosperity, and support new lifesaving breakthroughs for the citizens of the United States and around the world.

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