Hot Topic Discussion

Cancer's New Normal

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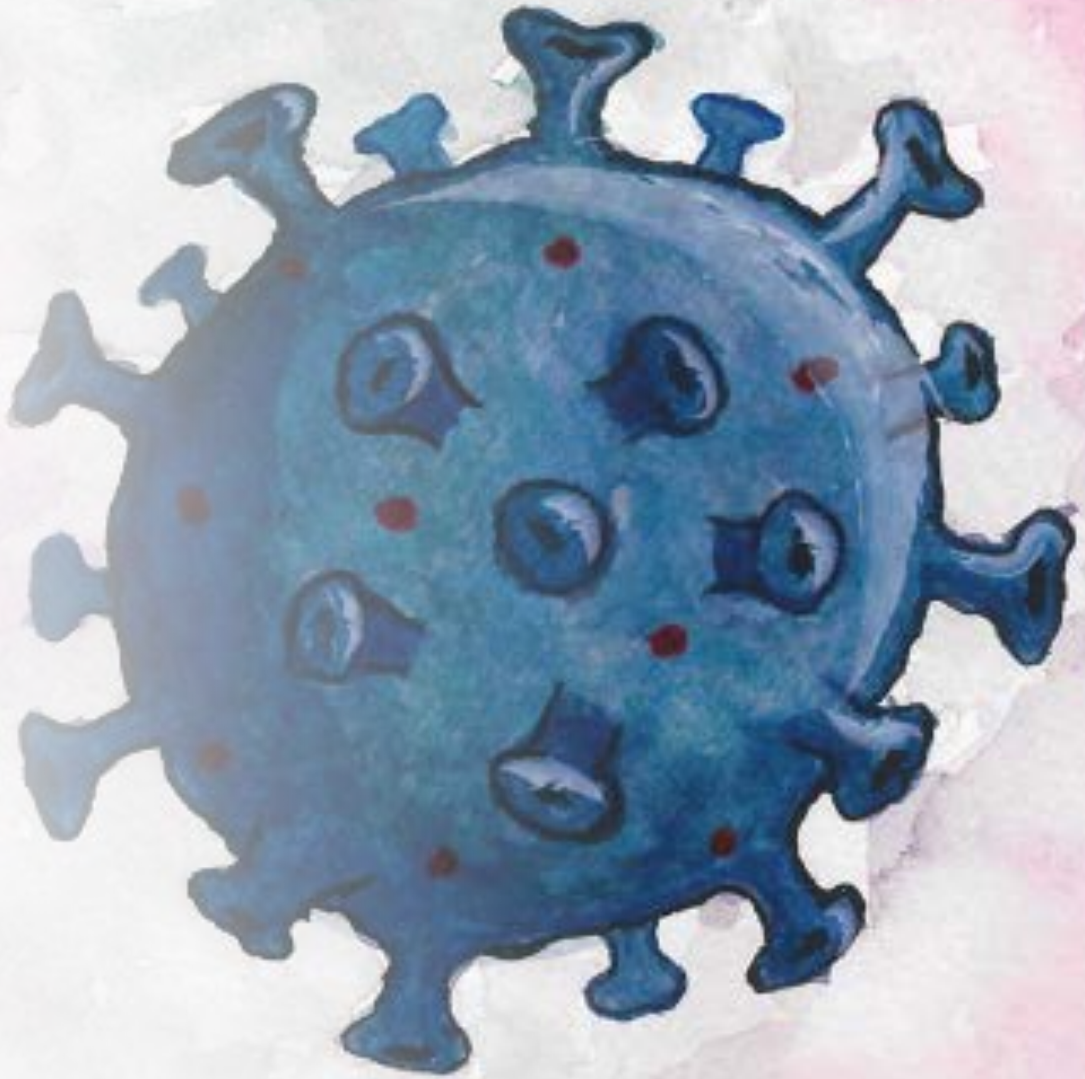
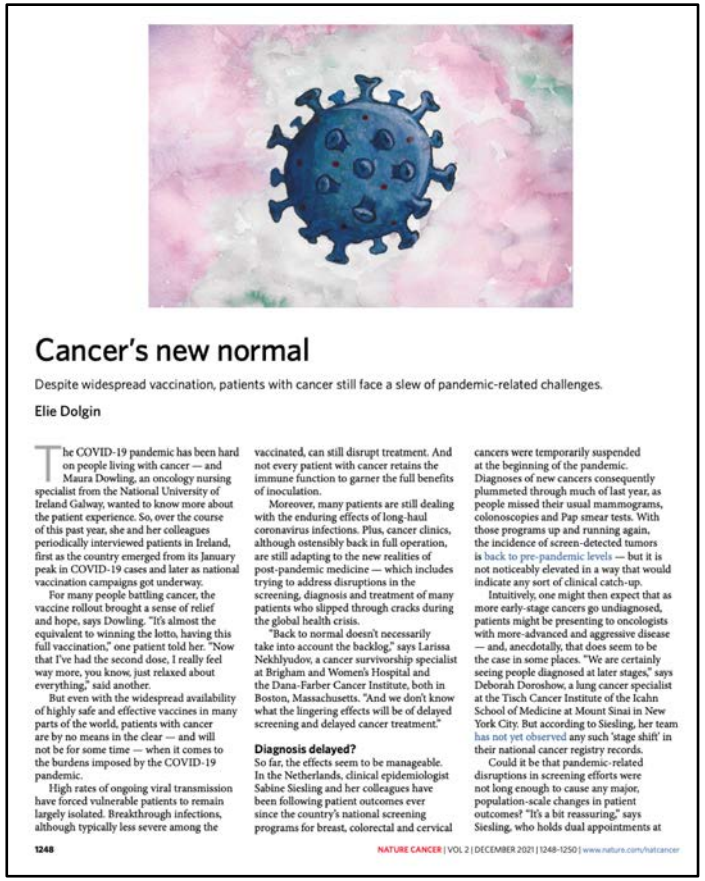
MARBLE CENTER FOR CANCER NANOMEDICINE



Dolgin, E. Cancer's new normal. *Nat Cancer* **2,** 1248–1250 (2021)

Why is this a Hot Topic?



Cancer's new normal

Despite widespread vaccination, patients with cancer still face a slew of pandemic-related challenges.

Elie Dolgin

The COVID-19 pandemic has been hard on people living with cancer — and Maura Dowling, an oncology nursing specialist from the National University of Ireland Galway, wanted to know more about the patient experience. So, over the course of this past year, she and her colleagues periodically interviewed patients in Ireland, first as the country emerged from its January peak in COVID-19 cases and later as national vaccination campaigns got underway.

For many people battling cancer, the vaccine rollout brought a sense of relief and hope, says Dowling. "It's almost the equivalent to winning the lotto, having this full vaccination," one patient told her. "Now that I've had the second dose, I really feel way more, you know, just relaxed about everything," said another.

But even with the widespread availability of highly safe and effective vaccines in many parts of the world, patients with cancer are by no means in the clear — and will not be for some time — when it comes to the burdens imposed by the COVID-19 pandemic.

High rates of ongoing viral transmission have forced vulnerable patients to remain largely isolated. Breakthrough infections, although typically less severe among the vaccinated, can still disrupt treatment. And not every patient with cancer retains the immune function to garner the full benefits of inoculation.

Moreover, many patients are still dealing with the enduring effects of long-haul coronavirus infections. Plus, cancer clinics, although ostensibly back in full operation, are still adapting to the new realities of post-pandemic medicine — which includes trying to address disruptions in the screening, diagnosis and treatment of many patients who slipped through cracks during the global health crisis.

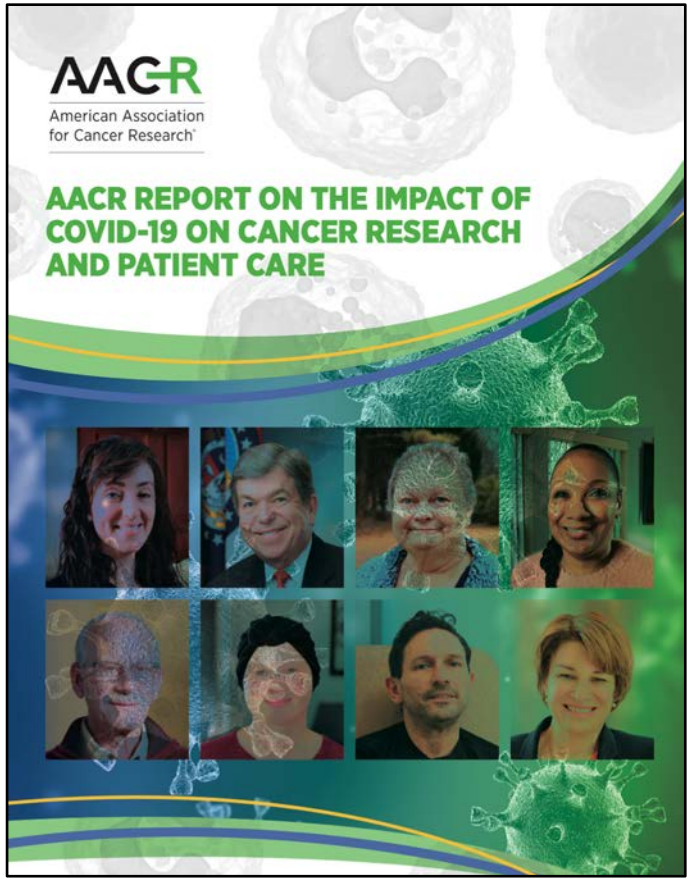
"Back to normal doesn't necessarily take into account the backlog," says Larissa Nekhlyudov, a cancer survivorship specialist at Brigham and Women's Hospital and the Dana-Farber Cancer Institute, both in Boston, Massachusetts. "And we don't know what the lingering effects will be of delayed screening and delayed cancer treatment."

Diagnosis delayed?

So far, the effects seem to be manageable. In the Netherlands, clinical epidemiologist Sabine Siesling and her colleagues have been following patient outcomes ever since the country's national screening programs for breast, colorectal and cervical cancers were temporarily suspended at the beginning of the pandemic. Diagnoses of new cancers consequently plummeted through much of last year, as people missed their usual mammograms, colonoscopies and Pap smear tests. With those programs up and running again, the incidence of screen-detected tumors is back to pre-pandemic levels — but it is not noticeably elevated in a way that would indicate any sort of clinical catch-up.

Intuitively, one might then expect that as more early-stage cancers go undiagnosed, patients might be presenting to oncologists with more-advanced and aggressive disease — and, anecdotally, that does seem to be the case in some places. "We are certainly seeing people diagnosed at later stages," says Deborah Doroshow, a lung cancer specialist at the Tisch Cancer Institute of the Icahn School of Medicine at Mount Sinai in New York City. But according to Siesling, her team has not yet observed any such 'stage shift' in their national cancer registry records.

Could it be that pandemic-related disruptions in screening efforts were not long enough to cause any major, population-scale changes in patient outcomes? "It's a bit reassuring," says Siesling, who holds dual appointments at



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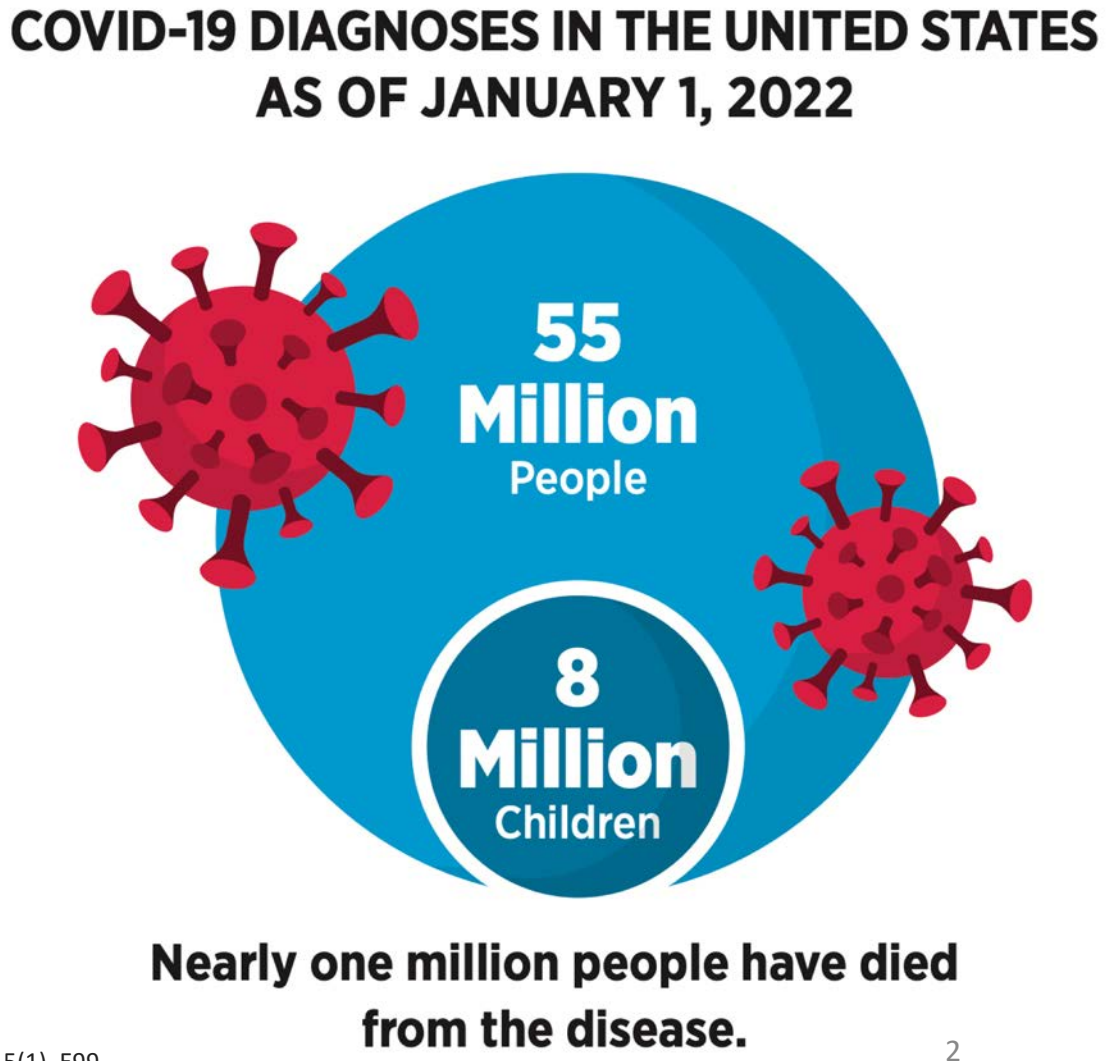
Understanding the COVID-19 Pandemic

- **5.4 million deaths** and more than **289 million cases worldwide**
- Disproportionate impact on Black, Indigenous, and Latinx communities has served to **further magnify the health inequities** in access and treatment that persist in our communities.
- FDA has approved/authorized **3 vaccines** against COVID-19.
- **64%** of the U.S. population has been fully vaccinated as of February 2022.



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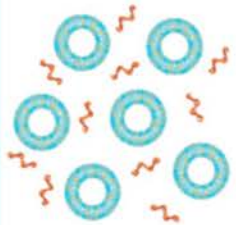
Nana-Sinkam, P., et al. (2021). Health disparities and equity in the era of COVID-19. Journal of Clinical and Translational Science, 5(1), E99.
https://usafacts.org/visualizations/covid-vaccine-tracker-states/

A Timeline of Innovation for RNA Vaccines

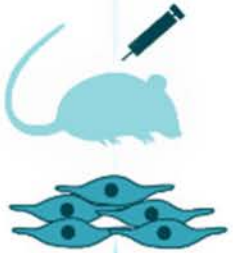
1961: *Brenner, Jacob, Watson, Meselson* mRNA Isolation

1964: *Bangham* Thin Film Hydration method launching liposome industry

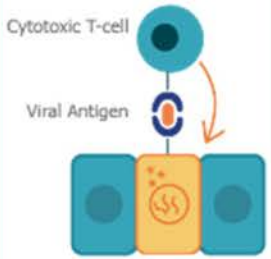
1987: *Felgner et al* Lipofection



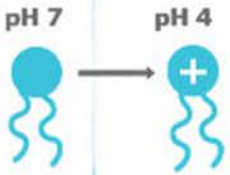
1990: *Wolff* mRNA injection in mouse muscle shows protein expression



1993: *Martinion* mRNA vaccine determines CTL response is antigens specific



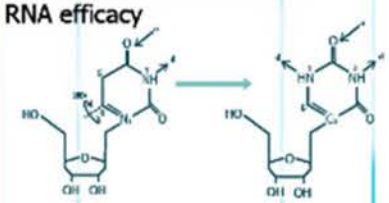
1994: *Bailey and Cullis* ionizable cationic lipid DODAP for lipofection



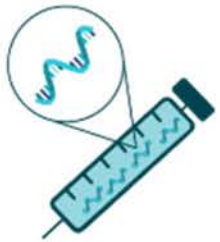
1995: *Conry* Efficacy study of mRNA vaccine in tumor model

2005: Jeffs et al publish T-tube method for plasmid-loaded LNPs

2005: Kariko & Weissman Base modification enhances RNA efficacy



2008: Weide & Pascolo FDA authorize clinical trial of direct injection RNA Vaccine

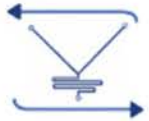


2010: Semple et al publish ionizable cationic lipids for next generation LNPs

2011: Kreiter Flt3 improves RNA vaccine efficacy

2012: Geall et al Demonstration of saRNA-LNP vaccine

2012: Beliveau et al publish microfluidic method for making siRNA LNPs:



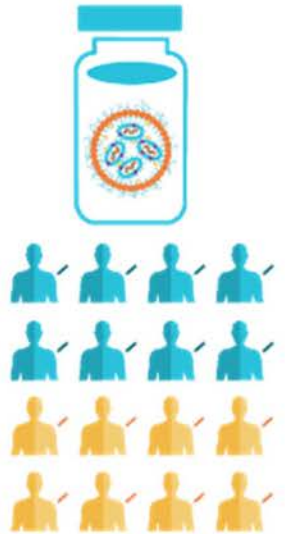
2013: Pollard Type I IFN reduces RNA efficacy by s.c. administration

2013: Hekele et al. First demonstration of saRNA-LNP for rapid response

2017: Bahl et al – First in human trial of mRNA-LNP vaccine (influenza)

2018: Onpattro: First RNA-LNP Therapeutic Approved by FDA

2020: Phase 3 clinical trials of multiple mRNA-LNP vaccine



2020: UK approved mRNA-LNP vaccine for SARS-CoV-2

1960s - 80s | 1990s | 2000s | 2010s | 2020

Source: Blakney, A.K. et al. (2021) An Update on Self-Amplifying mRNA Vaccine Development. Vaccines, 9(2), 97.

Impact of COVID-19 on Cancer Care

Delay in cancer screening

- **~100 million Cancer screening tests were not performed** in Europe during the pandemic.
- **1 in every 5 cancer patients** in Europe is currently still not receiving the surgical or chemotherapy treatment they need.
- It will take years to determine the full magnitude of these impacts

Impact on clinical trials

- **60 % decrease** in the number of new cancer clinical trials launched from January 2020 to May 2020 compared to the pre-pandemic period
- **70 %** of patients offered the opportunity to enroll in a clinical trial declined to do so because of the **fear of increased COVID-19 exposure**

Vulnerable patients

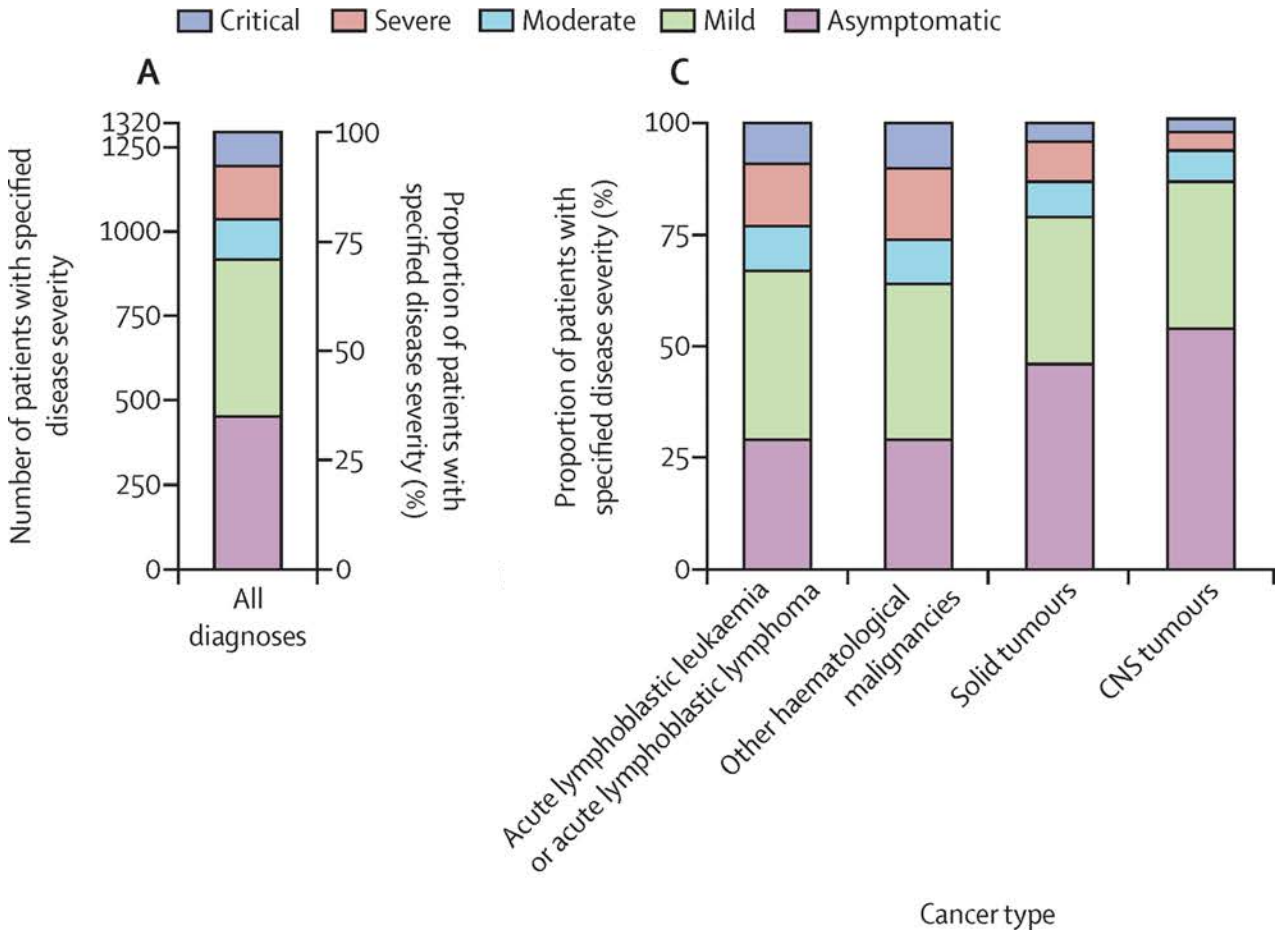
Many cancer patients have a **weakened immune system** and are at a higher risk of COVID-19 infection and severe disease.

In the U.S., the risk of COVID-19 infection was **7x higher** in patients diagnosed with cancer in 2020 compared to those with no history of cancer.

Sources:
https://www.europeancancer.org/resources/201:time-to-act.html
Chen RC, Haynes K, Du S, Barron J, Katz AJ. Association of Cancer Screening Deficit in the United States With the COVID-19 Pandemic. JAMA Oncol. 2021;7(6):878–884.
Lee LYW, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. The Lancet. 2020;395(10241):919–926.
AACR Report on the Impact of COVID-19 on Cancer Research and Patient Care. Published February 9, 2022.

Globally, COVID Takes A Harsher Toll On Children with Cancer

- The COVID-19 pandemic has considerably **affected pediatric oncology services worldwide**, posing substantial disruptions to cancer diagnosis and management, particularly in low-income and middle-income countries.
- Of the kids with cancer, **20%** had a severe critical infection with COVID. And death occurred in about **4% of all patients** – considerably greater than the general pediatric population with COVID-19.



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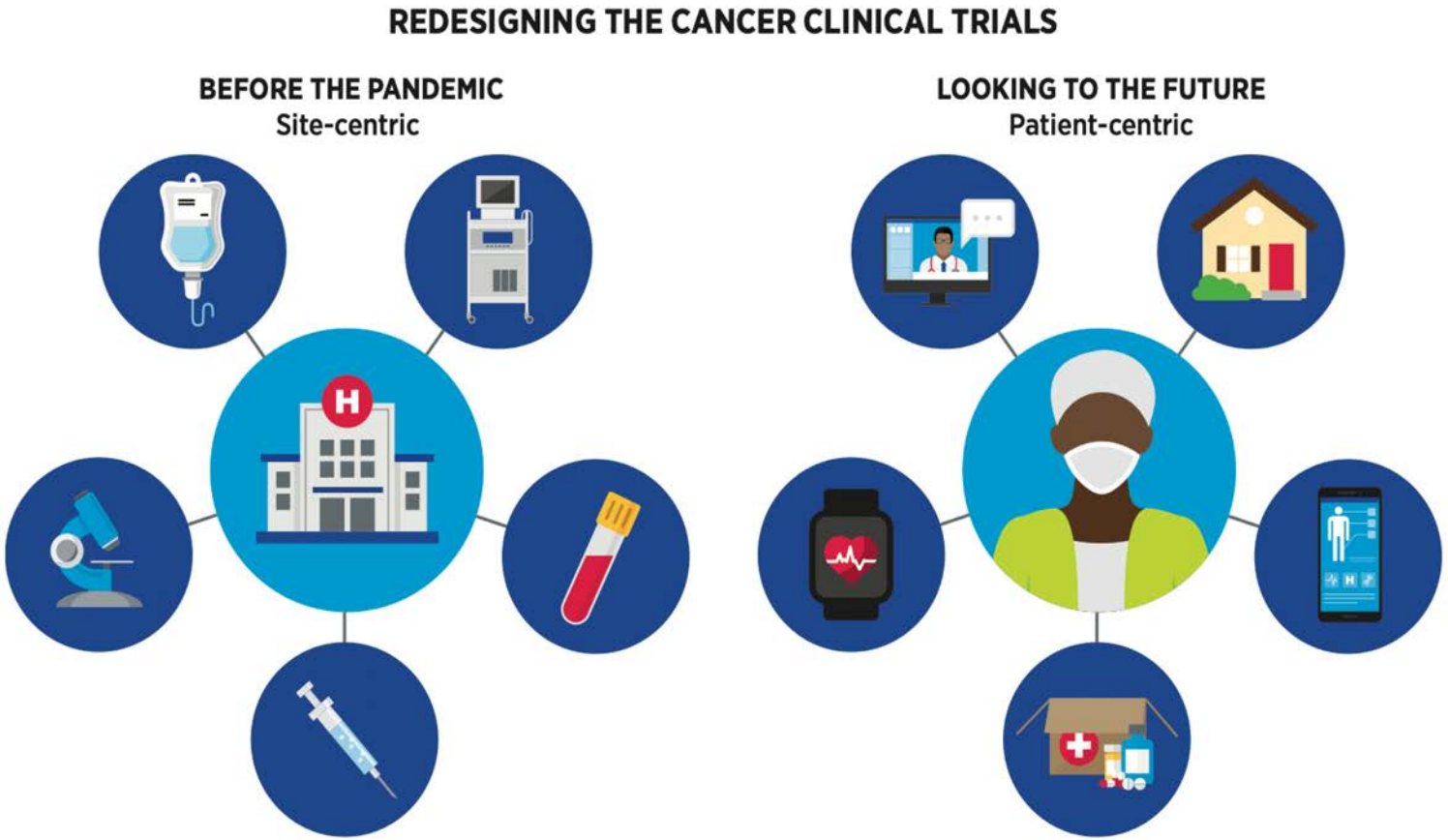
Graetz, D., et al. Global effect of the COVID-19 pandemic on pediatric cancer care: a cross-sectional study. The Lancet. 2021; 5(5):332–340.
Mukakda, D., et al. Global characteristics and outcomes of SARS-CoV-2 infection in children and adolescents with cancer (GRCCC): a cohort study. The Lancet. 2021; 22(10):1426.

Cancer's New Normal: What's here to stay

- **Telehealth + digital health** to streamline patient experience, including clinical trials.
- **Reform regulatory paths:** dosing schedules due to less hospital visits, bring trials to patients.
- **Modifications in cancer screening and treatment regimens:** long term studies needed to determine whether such changes improve overall patient survival.



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New Research opportunities in Oncology

- **A framework for collaborations and sharing resources**– reinvigorating collaborative initiatives (Breakthrough Cancer, Lung Ambition Alliance, Cancer Moonshot, etc.)
- **Sequencing technologies**.
- **Repurposing** anti-cancer drugs.
- **Linkage** between **infection** and **cancer**.
- **RNA** cancer vaccines.
- **Drug delivery** (AAV and non-viral).
  - Renewed interest and enthusiasm for nanoparticle drug delivery across a range of applications

Source:

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Discussion

- How has the pandemic effected your research?
- Do you think health literacy has increased?

  mRNA vs protein *booster vs additional dose*

  Phase I/II/III clinical trial *statistical vs clinical significance*
- Do you think cancer patients will be more or less likely to engage in clinical trials going forward?
- Do you think the path for FDA approval of nanotechnologies will change?
- Do you think funding and patient advocacy groups will focus more on nanotechnology?

Image: https://www.medpagetoday.com/infectiousdisease/covid19/87002

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