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THE CANCER LETTER

Inside information on cancer research and drug development

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CANCER CRUSADE TELLS THE GRIPPING STORY OF THE NATIONAL CANCER ACT

First published in 1977, Cancer Crusade: The Story of the National Cancer Act of 1971, is a dispassionate legislative history—a book you can trust.

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University of New Mexico Comprehensive Cancer Center

The University of New Mexico Comprehensive Cancer Center is the Official Cancer Center of New Mexico and the only National Cancer Institute-designated Cancer Center in a 500-mile radius. Its 146 board-certified oncology specialty physicians include cancer surgeons in every specialty (abdominal, thoracic, bone and soft tissue, neurosurgery, genitourinary, gynecology, and head and neck cancers), adult and pediatric hematologists/medical oncologists, gynecologic oncologists, and radiation oncologists. They, along with more than 600 other cancer healthcare professionals (nurses, pharmacists, nutritionists, navigators, psychologists and social workers), provide treatment to 65% of New Mexico's cancer patients from all across the state and partner with community health systems statewide to provide cancer care closer to home. They treated approximately 13,000 patients in more than 100,000 ambulatory clinic visits in addition to in-patient hospitalizations at UNM Hospital. A total of nearly 1300 patients participated in cancer clinical trials, 40% of whom participated in clinical trials testing new cancer treatments that include tests of novel cancer prevention strategies and cancer genome sequencing. The more than 100 cancer research scientists affiliated with the UNMCCC were awarded $36.2 million in federal and private grants and contracts for cancer research projects. Since 2015, they have published nearly 1000 manuscripts, and promoting economic development, they filed 136 new patents and launched 10 new biotechnology start-up companies. Finally, the physicians, scientists and staff have provided education and training experiences to more than 500 high school, undergraduate, graduate, and postdoctoral fellowship students in cancer research and cancer health care delivery. Learn more at cancer.unm.edu.

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EDITORIAL

Summer reading issue 2021: Reflecting on two years of reckoning

By Matthew Bin Han Ong

Two years have gone by since we put together our first summer reading issue in 2019—and by the gods, what a ride these two years have been!

Earlier this year, to mark the 50th anniversary of the signing of the National Cancer Act, we launched the Cancer History Project, an interactive, authoritative resource designed to preserve the history of cancer research and to spark rigorous discussion of the achievements of the past half-century.

That said, celebratory recollections of history are incomplete if they don't reflect the fact that millions of Americans are unable to benefit from advances made in oncology over five decades. Indeed, what's biomedical leadership on the global stage without leadership at home?

The past two years have been a time of reckoning and change—spurred by a national awakening on social justice and by a deadly pandemic—not to mention pulling away, multiple times, from the brink of political destabilization.

Health equity, both in the public consciousness and among professionals who provide care, is finally considered a matter requiring the highest degree of attention. It's also a federal priority, as the Biden administration has issued a call to action on cancer disparities, and as Congress designates funds to boost cancer research and develop equity initiatives.

We have the privilege to document this reckoning week after week in *The Cancer Letter*, and—with collaboration from leading cancer institutions—to place today's events in context through the Cancer History Project.

Last week, we convened our first-ever panel—led by Otis Brawley, co-editor of CHP, and Bloomberg Distinguished Professor of Oncology and Epidemiology at Johns Hopkins University—which focused on the three comprehensive cancer centers that shaped the NCI Cancer Centers Program. A recap appears on page 38.

In this issue, we have the honor to bring back the electronic version of *Cancer Crusade; The Story of the National Cancer*

Act of 1971, the authoritative account of the legislative history of the National Cancer Act, written by political scientist Richard A. Rettig.

The book, published shortly after the pivotal law was enacted, is available for free through the Cancer History Project. A new foreword by Brawley and *The Cancer Letter* Editor and Publisher Paul Goldberg appears on page 7.

Also in this issue, we reprise the reading list we started last year—the 2021 list appears on page 11. Thank you to the diverse panel of clinicians, basic scientists, early-career faculty, and regulators for submitting your book recommendations, many of which focus on leadership and systemic racism.

As a publication of record, we've charted a course for coverage that we hoped would ignite conversations at healthcare institutions and drive policies that would improve equity.

Alexandria Carolan led the charge on gender equity in a series on bias and sexual misconduct that was a *tour de force* two years in the making, beginning with a story about how women in oncology are stripped of their titles when they are introduced.

We followed up with a survey in 2020, finding that women who experienced gender bias and sexual harassment in academic medicine unanimously rated their institutions' response as inadequate.

In May, her investigation into sexual misconduct by an oncologist, Axel Grothey, sparked a groundswell of indignation and calls for accountability. A provision moving through Congress may soon prevent perpetrators from escaping public scrutiny, by requiring institutions to report misconduct to NIH.

In June, we embarked on extensive reportage on cancer disparities and the disenfranchisement of minorities in health care—and what cancer centers are doing to advance diversity, equity, and inclusion—spearheaded by yours truly, in collaboration with the Association of Health Care Journalists and The Commonwealth Fund.

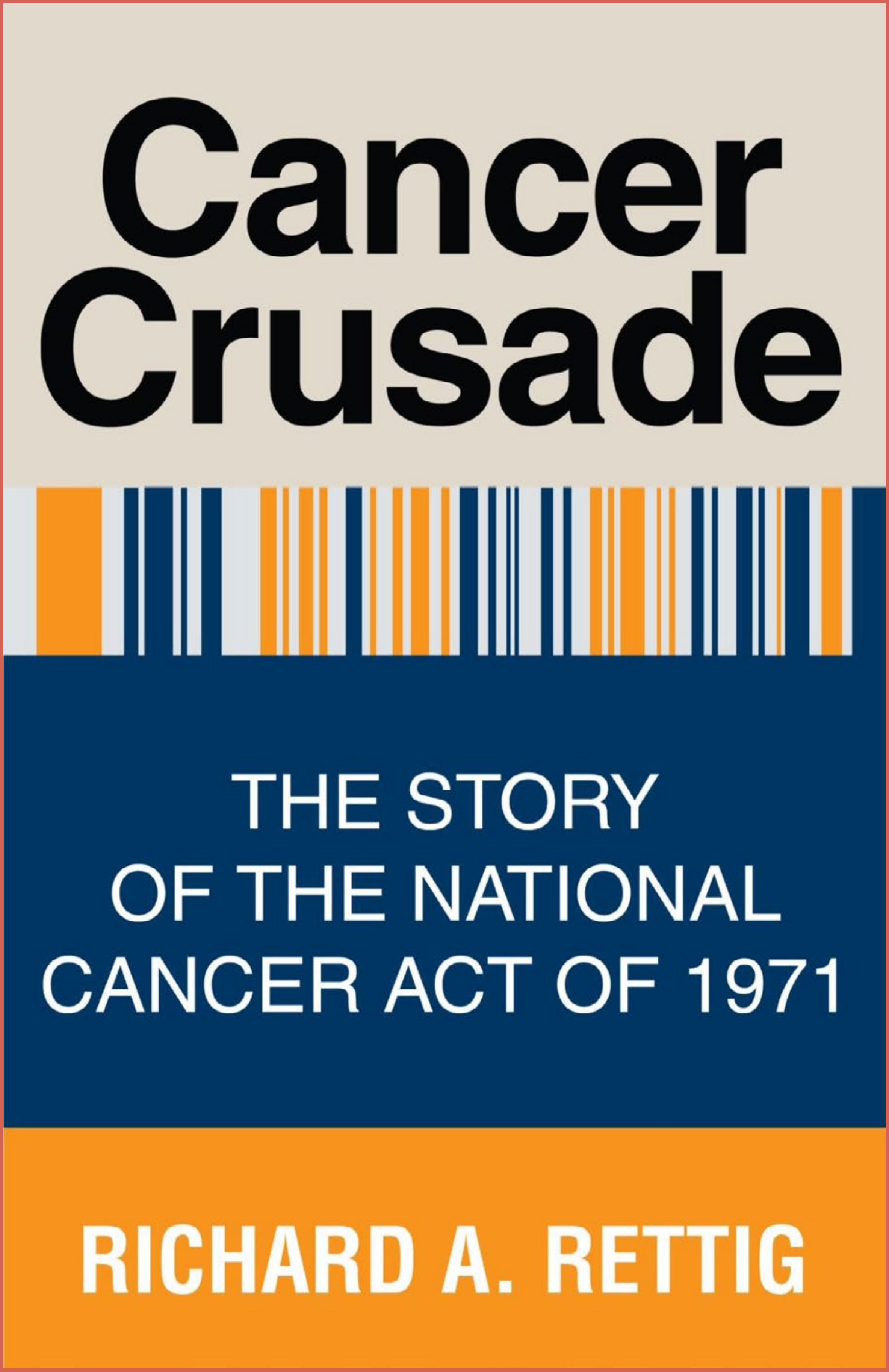
> “Celebratory recollections of history are incomplete if they don't reflect the fact that millions of Americans are unable to benefit from advances made in oncology over five decades.”

This year's coverage builds on a series of stories in 2020, including a leadership pipeline survey conducted by *The Cancer Letter* and the Association of American Cancer Institutes. We are examining, in meticulous detail, the underrepresentation of racial and ethnic minorities, not only in the workforce at academic cancer centers and NCI, but also among patients across an overwhelming proportion of U.S. hospitals.

The 2021 series on health equity appears here.

As our work on these topics continues, we hope you take a step back as the summer winds down to reflect on the state of oncology with us—or pour yourself a libation of your choice and read Proust.

The Cancer Letter is taking a publication break. We will return on Sept. 3.



Cancer Crusade

THE STORY OF THE NATIONAL CANCER ACT OF 1971

RICHARD A. RETTIG

CANCER HISTORY PROJECT

Cancer Crusade tells the gripping story of the National Cancer Act

By Otis Brawley and Paul Goldberg

First published in 1977, *Cancer Crusade: The Story of the National Cancer Act of 1971*, is a dispassionate legislative history—a book you can trust.

To put it simply, anyone who wishes to understand the events that half a century ago created the modern cancer program should turn to this authoritative book. With permission of the author, Richard A. Rettig, *Cancer Crusade* can be downloaded on the Cancer History Project's website.

Two other books published on CHP are:

- *Stairway of Surprise*, a previously unpublished memoir by Charles Gordon Zubrod
- *Simone's Maxims*, by Joseph V. Simone

It's hard to miss the fact that echoes of the debates that rocked the medical establishment during the buildup to a the National Cancer Act continue can be heard to this day:

- Rettig tells us about tensions between NIH and NCI, stemming from assertions of independence of the cancer program. (You can see this theme play out in the first issue of *The Cancer Letter* and, with clock-like regularity, thereafter.)
- Rettig recounts debates about direction of funds and relative merits of grants vs. contracts. (You will find discussion of the subject in Otis Brawley's conversation with directors of Roswell Park Cancer Center, Memorial Sloan Kettering Cancer Center, and MD Anderson Cancer Center. The conversation appears on page 38.)
- Rettig tells us about strident political rhetoric comparing the "conquest of cancer" with the triumphs of American engineering—the Manhattan Project and, of course, the moonshot. (The argument about the relative roles of science and engineering now involves the Biden Administration's proposal to create Advanced Research Projects Agency for Health, or ARPA-H.)

Rettig is not a journalist, not a biographer, not a historian. He is a political scientist writing a smart legislative history. And yet, the characters in his story are so formidable and his narrative so rich that *Cancer Crusade* acquires the characteristics of a work of journalism, biography, history—and, of course, political science.

"When I was a graduate student at MIT, in political science, I encountered NIH and its role in the American healthcare system. The encounter was in analysis of [NIH] in political terms," Rettig said to us recently. He was particularly intrigued by the NIH Director James Shannon, his deputies, and their relationships to the key members of Congress, especially on appropriations.

Shannon, a gigantic presence in this book, is a physician who had done work in malaria and kidney function, who served as NIH director from 1955 to 1968, presiding over a rapid expansion of biomedical research. That period is known interchangeably as "the Shannon years" and "the Golden Age."

The pressure on Congress to dramatically increase appropriations for NIH came largely from outside the medical establishment, from a group of wealthy socialites who were galvanized into action by the philanthropist Mary Lasker. The group also included the cancer pioneer Sidney Farber and the heart surgeon Michael DeBakey.

Mary was the widow of Albert Lasker, the founder of modern American public relations and creator of a variety of national brands of consumer products, including—problematically—Lucky Strike cigarettes.

Lasker et al. sought to inspire the academic establishment to set its sights higher, to go for the cures.

"I am opposed to heart attacks and cancer and strokes the way I am opposed to sin," Lasker has famously said. A masterful manipulator with a special talent for arranging mirrors to create desired illusions, Lasker had access to Democratic presidents and legislators, including, notably, the Kennedys. Thanks to YouTube, you can hear her conversation with Lyndon and Lady Bird Johnson.

The Laskerites felt the cure for cancer could be easily accomplished if there was money to fuel research. Research required money.

In the 1950s what cancer research that existed was funded by philanthropy and clinical revenues. The idea of government funding medical research was rare, and government-funded medical research was often done through government contracts and governed by the same rules and regulations that the government used to buy bombers and warships.

Someone in government specified what was needed and negotiated getting it done. The idea of an investigator-initiated grant, a scientist in a university having an idea for research and getting it funded was not widely used and not accepted in many parts of the NIH. The National Cancer Act would change that.

It has been said, albeit with scant documentation, that the Lasker's American Cancer Society funded more research grants than the government in the 1950's. Lasker used the talents learned from her husband, Albert, to build a field army of advocates in communities across the U.S. Theirs was a movement to get the government into funding cancer research. The feeling was that the government had deep pockets and only the government could launch a sustained research effort.

Rettig became interested in the Shannon-Lasker concerto while he was still at MIT, he said.

"The hook got set early, independent of cancer, and early recognition of the role of Mary Lasker and her allies. Those were the antecedents to this," Rettig said. With the buildup to the National Cancer Act, "cancer became the dominant motivating enemy to be vanquished," Rettig said. The memory of this landmark law was still fresh, and the story was Rettig's to tell.

About half of *Cancer Crusade* chronicles the legislative history of the National Cancer Act and the interplay between two archenemies—Kennedy and Richard M. Nixon. Rettig doesn't gauge whether there was indeed a groundswell of grassroots support that led politicians to be interested in a cancer effort. Anecdotally, we know that in the hustings, comparisons were heard of how much money was spent on cancer, compared to other government programs.

Kennedy's career had suffered a catastrophic setback in July 1969, when a car he was driving went off a bridge on Chappaquiddick Island, killing Mary Jo Kopoechne, a young woman who had been working on Robert Kennedy's campaign. Ted Kennedy won reelection to his Senate seat, but lost his position as the Majority Whip.

Kennedy needed an issue that could propel him to presidency in 1972. There was, clearly, an opportunity.

Initially, the Laskerites had been relying on Sen. Ralph Yarborough to develop their cancer bill. Yarborough had convened a "panel of consultants," which issued a report calling for bold action on cancer.

Alas, Yarborough lost his Senate seat, and under normal circumstances, the effort to develop a bill would have been stalled at the end of 1970. For Kennedy, this was an opportunity to jump in and lead.

"Nixon got deeply involved because of Kennedy," Rettig said to us, recapping his book's key argument. "He didn't want yet another Kennedy to mar his political career. Nixon feared Kennedy, from his experience with late Jack Kennedy, and was not about to let another Kennedy influence and wreck his own political career. And so, that was a very important precipitating factor in the president's involvement in this."

The Kennedy bill, optimistically called the Conquest of Cancer Act, proposed giving the cancer program unprecedented autonomy, including pulling NCI out of NIH.

Shannon, by then a former NIH director, was strongly opposed to this idea. The Laskerites have gone too far, Shannon wrote at the time:

> The creation of an independent Cancer Authority, removing the NCI from the ambit of the NIH, would, in my opinion, not accomplish anything that could not be done within

present NIH processes, or trivial and easily realized modifications thereof. On the other hand, it would unleash forces of a divisive character which would quickly destroy the integrity of the NIH. I predict that in a very short time, orderly governance would be replaced by anarchy, and that instead of a judiciously balanced program of biomedical research, program emphasis would be entirely determined by uncritical zealots, by experts in advertising and public relations, and by rapacious "empire builders." These latter forces are not to be disdained and they have played an invaluable role in the past quarter century in making the lay public aware that, through research, there was a real possibility of realizing inchoate public hopes and aspirations to control disease. As forces modulating the scientific judgment process, their contributions have been positive and important. As determinants, however, I would expect them to create chaos.

Ultimately, through compromise, the National Cancer Act was softened, leaving NCI within NIH, but giving it unique authorities that include the Bypass Budget and presidential appointment of NCI directors. (No other NIH institute or center is run by a presidential appointee). Unique authorities also include the President's Cancer Panel, which is designed to have direct access to the president.

At the signing of the NCA, on Dec. 23, 1971, a sense of optimism could be felt in the room. Some congressmen seriously discussed cancer being cured by America's bicentennial—by July 4, 1976. Indeed, if the U.S. could build an atomic bomb, if the U.S. could put a man on the moon, the U.S. could cure cancer.

The NCA, as signed by President Nixon, created a "National Cancer Program" led by the presidentially appointed director of the National Cancer Institute. The act also created:

- **The National Cancer Advisory Board**. The NCAB members are appointed to four year terms by the president. The board does secondary review of grants to be funded by the National Cancer Institute. To this day, representatives of other government agencies involved in cancer have non-voting seats on the NCAB examples include the FDA, CDC, Veterans Administration, Environmental Protection Agency.
- The concept of **NCI-designated cancer centers**. Previously, there were self-designated cancer centers, some were recognized by NCI but there was no "NCI designation." The Association of American Cancer Institutes, started in 1959, was a major supporter of the movement for a National Program.
- A formal **NCI drug development program**.
- A mandate for a **cancer control program**. This was manifest through:
    - A directive for the NCI to provide cancer information and education. This led to the Cancer Information Service, and is seen today in such things as Physician Data Querry and **PDQ.**
    - A requirement for maintenance of population data. This led to the **Surveillance Epidemiology and End Results Program.**
    - Creation of the Division of Cancer Prevention and Control.

The act reemphasized and expanded support for the clinical trials groups, which were, for the most part, formed in the 1950s and early 1960s.

At its core, the law provided increased support for cancer research around the country and made the NCI Director pivotal to the country's cancer effort. In terms of appropriations, the law was a huge success.

At the time of the signing of the NCA, the NCI budget was just $149 million. By 1979, it had grown to $940 million.

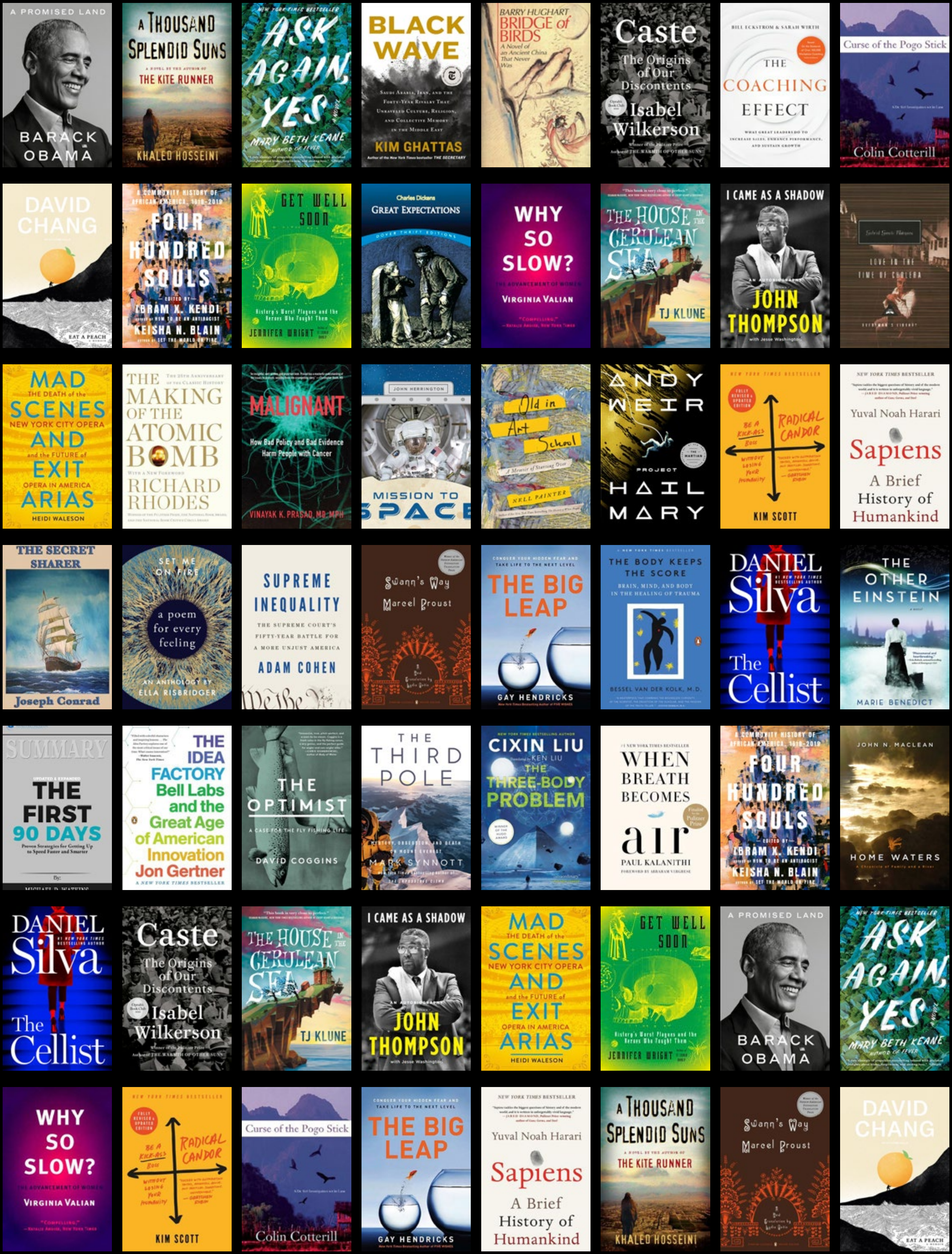
The growth can be seen below:

- 1971: $149 million
- 1979: $940 million
- 1992: $1.8 billion
- 1998: $2.6 billion
- 2002: $4.2 billion
- 2010: $5.1 billion
- 2015: $4.95 billion
- 2017: $5.64 billion
- 2021: $6.56 billion

The growth resulted in dramatic increases in the grant funding, primarily to universities, in the extramural community. Today, 73% of the NCI budget is for grants. The request for application (RFA) is a grant mechanism that allows ACS to request investigator-initiated proposals in areas the Institute sees a need. It is currently 18% of the NCI budget.

Whether they realized it or not, the politicians and advocates who clashed over the legislative sausage-making Rettig describes in *Cancer Crusade* had, in fact, built the launching pad for the National Cancer Program's ultimate takeoff.

Cancer Crusade is available on the Cancer History Project as a free download, as a PDF or e-book. A print version is available here.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BARACK OBAMA
A THOUSAND SPLENDID SUNS
THE KITE RUNNER
KHALED HOSSEINI
ASK AGAIN, YES
MARY BETH KEANE
BLACK WAVE
KIM GHATTAS
BARRY HUGHART
BRIDGE of BIRDS
A Novel of an Ancient China That Never Was
Caste
The Origins of Our Discontents
Isabel Wilkerson
BILL ECKSTROM & SARAH WIRTH
THE COACHING EFFECT
Curse of the Pogo Stick
Colin Cotterill
DAVID CHANG
EAT A PEACH
A COMMUNITY HISTORY OF AFRICAN AMERICA, 1619–2019
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KEISHA N. BLAIN
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WHY SO SLOW?
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VIRGINIA VALIAN
THE HOUSE IN THE CERULEAN SEA
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AN AUTOBIOGRAPHY
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Swann's Way
Marcel Proust
DAVID CHANG
EAT A PEACH

BOOK REVIEW

What are you reading in 2021?

Are Ibram X. Kendi, Charles Dickens, and Nobel Laureate Paul Nurse on your bookshelf, too?

These are a few of the authors your colleagues are reading in 2021.

A diverse panel of clinicians, basic scientists, early-career faculty, and regulators submitted their book recommendations to *The Cancer Letter* for the second year in a row.

Non-fiction and fiction are equally represented, ranging from opera to Obama, Proust to fly fishing. This year's reading list genres have expanded to include a poetry anthology, a children's book, a podcast—and Wafik El-Deiry's in-depth review of seven books, which appears on page 23.

Last year's book recommendations told a story of a year filled with activism, grappling with the COVID-19 pandemic, and using fiction as an escape, perhaps in place of a much-needed vacation (*The Cancer Letter*, Aug. 6, 2020). The list seemed to want to answer the question: "What the hell is going on?"

This year's list demonstrates an evolution of thought: stories of personal and professional growth, the challenge of becoming a better leader, and deeper explorations of systemic racism in the U.S. All that, plus a passion for a good book—and fly fishing.

If the question last year was "What the hell is going on," this year's question appears to be, "How can we be better?"

Fumiko Ladd Chino, MD

Radiation oncologist,
Memorial Sloan Kettering Cancer Center

- ***Malignant: How Bad Policy and Bad Evidence Harm People with Cancer***, by Vinayak K. Prasad, MD, MPH
- ***Bridge of Birds: A Novel of an Ancient China That Never Was***, by Barry Hughart

Dr. Prasad walks us through the flawed process of oncology drug clinical trial design, approvals, and marketing, highlighting with each step the multiple ways that our current healthcare structure fails our patients and fosters high costs.

With a keen mind (and #SoMe rabble-rouser credentials), Prasad has made a name for himself as a champion for restraint in a cancer industry hype machine that often over promises and under delivers meaningful outcomes.

Before I knew what "culture appropriation" was, I fell in love with this China-themed fantasy novel about a magical adventure filled with mystery and mayhem. The characters are dynamic and rich, the plot is fast-paced and captivating, and the dialogue is witty and engaging. I tend to re-read it once a year, and after 20-odd reads, it still delivers with humor, heart, and a conclusion with enough emotional heft to (literally) bring me to tears each time.

Toni K. Choueiri, MD

Director, Lank Center for Genitourinary Oncology, Department of Medical Oncology, Dana-Farber Cancer Institute; Co-Leader, Kidney Cancer Program, Dana-Farber/Harvard Cancer Center; Jerome and Nancy Kohlberg Professor of Medicine, Harvard Medical School

- ***Black Wave***, by Kim Ghattas
- ***Love In The Time Of Cholera***, by Gabriel García Márquez

I am currently finishing two books, quite different in material and topic:

Black Wave (by Kim Ghattas): a fascinating "big picture" book that weaves together history, politics, and culture to deliver a gripping vivid story about the Middle East since 1979. It is a masterpiece that is based on extensive historical research and on-the-ground reporting from the author.

To me, this is an essential book for anyone interested in understanding the forces shaping the Middle East today. It struck a chord with me, as I share a similar background as the author and I grew up in the middle of this geopolitical drama.

Love In The Time Of Cholera (By Gabriel García Márquez): One of the best works of Nobel prize Laureate "Gabito". It explores the solitude of the individual and of humankind. In this novel, the existential anguish of feeling alone is portrayed through the solitude of love.

Both love and cholera are so intertwined in this novel because love can be as intense as cholera and can take many faces: jealousy, agony, obsession, desire, pity, aging, suffering and vengeance. Is it love after all?

Deborah Doroshow, MD, PhD

Assistant professor of medicine, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai

- ***Ask Again, Yes***, by Mary Beth Keane

I have always found that reading fiction helps me stay a bit more balanced and fulfilled. As a historian specializing in families and mental illness in the 20th century (I have a PhD in American history in addition to my day job as an oncologist), I often find myself drawn to multigenerational narratives that illustrate changing social and cultural norms.

Mary Beth Keane's *Ask Again, Yes* (Scribner, 2019) is a beautifully written portrayal of two intertwined families living in and around New York City from the 1970s to the present. As so many good domestic novels do, Keane explores themes of love, career, betrayal, and forgiveness, all while portraying mental illness and physical disability with great sensitivity. I couldn't put it down.

Wafik S. El-Deiry, MD, PhD

American Cancer Society Research Professor, Director, Cancer Center at Brown University; Director, Joint Program in Cancer Biology, Brown University and Lifespan Cancer Institute; Attending physician, hematology/oncology, LCI, Mencoff Family University Professor, Brown University; Associate dean, Oncologic Sciences, Warren Alpert Medical School, Brown University

- ***What is Life? Five Great Ideas in Biology***, by Paul Nurse
- ***Guinea-Pig Doctors: The Drama of Medical Research Through Self-Experimentation***, by Jon Franklin and Jon Sutherland (out of print)

- ***Letter To A Young Female Physician: Notes from a Medical Life***, by Suzanne Koven
- ***Off Our Chests: A Candid Tour Through The World Of Cancer***, by John Marshall and Liza Marshall
- ***Editing Humanity: The CRISPR Revolution And The New Era Of Genome Editing***, by Kevin Davies
- ***100 Questions and Answers About Ovarian Cancer, 4th Edition***, by Don Dizon, Dorinda "Dee" Sparacio, and Vance Broach
- ***Rethinking Cancer: A New Paradigm for the Post-Genomic Era***, by Bernhard Strauss, Marta Bertolaso, Ingemar Ernberg, and Minna J. Bissell

A full review of El-Deiry's recommendations appears on page 23.

Lola A. Fashoyin-Aje, MD, MPH

Medical oncologist, deputy division director, Division of Oncology 3, Office of Oncologic Diseases; Associate director, Science and policy to address disparities, Oncology Center of Excellence, FDA

- ***The Body Keeps the Score***, by Bessel van der Kolk

I am currently reading *The Body Keeps The Score*, by Boston-based Dutch psychiatrist and pioneering PTSD researcher Bessel van der Kolk, MD. The book provides a really fascinating, exceptionally well-presented, and in-depth examination of the impact of painful, traumatic experiences on our mental and physical health.

The author draws from the fields of developmental psychopathology, neuroscience, and neurobiology, and provides powerful, illustrative examples from his own work and that of others which renders the at times technical subject matter, quite accessible for the non-neuroscientist.

In reading this book, one appreciates the long lasting manifestations of traumatic experiences in all aspects of our life, but also the tangible ways that help begin the healing process.

Christopher Flowers, MD

Department chair, Department of Lymphoma/Myeloma, Division of Cancer Medicine, MD Anderson Cancer Center

- ***The Coaching Effect : What Great Leaders Do to Increase Sales, Enhance Performance, and Sustain Growth***, by Bill Eckstrom and Sarah Wirth
- ***Get Well Soon: History's Worst Plagues and the Heroes Who Fought Them***, by Jennifer Wright

Authors Bill Eckstrom and Sarah Wirth summarize decades of research on the behaviors, thought patterns, and activities that produce high performance among leaders. This research involved greater than 100,000 coaching interactions in the workplace.

The authors discuss three critical performance drivers and four high-growth activities that coaches utilize to build a high performing team. Eckstrom and Wirth describe in detail how leaders can measure and improve their coaching to lead their teams to better results. This resource can help leaders at all levels to help engage their colleagues and enable high performance across any organization.

Get Well Soon is an enthralling, witty and surprisingly prescient history of pandemic diseases. Throughout the course of this work, Jennifer Wright clearly describes the hazards of disease in ways that are thought-provoking and offer intriguing insights that have modern relevance.

This book details the plagues the planet has faced over several centuries and provides in depth stories of the heroic women and men who helped to overcome them.

This work provides an interesting mix of research and storytelling with intermittent humor and pop culture references, while never diminishing the tragedy of the lives lost. Her passion for humanity is evident throughout.

Karyn A. Goodman, MD, MS

Professor and vice chair for research and quality, Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai; Associate director for clinical research, Tisch Cancer Institute

- ***Sapiens: A Brief History of Humankind***, by Yuval Noah Harari

I just finished *Sapiens: A Brief History of Humankind* by Yuval Noah Harari. It was a 10,000 foot view of humanity from its nascence and divergence from our prehistoric ancestors to the development of modern society. While it is infused with the author's philosophy and interpretations of history, I found that Dr. Harari was able to easily weave together the various historical data available on the introduction of new ideas, science, and technology into a critical, but enlightening exposé of human history.

He breaks down the book into larger breakthroughs that have radically changed civilization through what he terms are the cognitive, agricultural, and scientific revolutions.

He has a unique perspective on how science, capitalism, racism, religion, and colonization, among others, intersect. I enjoyed the integration of so many aspects of human history into one book and after reading this, I am more aware of the intricate interplay between all of the influencing factors that brought humans to where we are today in the modern world.

Stephanie L. Graff, MD

Director of breast oncology, Lifespan Cancer Institute

- ***The First 90 Days: Proven Strategies for Getting Up to Speed Faster and Smarter***, by Michael D. Watkins
- ***Old In Art School: A Memoir of Starting Over***, by Nell Painter

I am often reading two books at once, normally loosely related, one data-heavy or learning-focused and one fun read.

With my recent career transition from community oncology to academia, I read *The First 90 Days*, which provided some remarkable insights into understanding a new culture quickly and building strategic alliances, as well as strategies for early wins. I particularly liked the FOGLAMP pneumonic for project checklists: Focus, Oversight, Goals, Leadership, Abilities, Means, & Processes. The book's constant reminder to say no to projects that did not align with your career goals was much needed reinforcement.

I paired *First 90 Days* with *Old in Art School*, because if Dr. Nell Painter can, at age 64, also manage a dramatic career transition successfully (coincidentally also intersecting the Ocean State), then surely, I can!

She explores the value of power, institutional support, aging, racism, and sexism—issues we face in medicine as well. The glimpse into the complex world of art and art world politics was interesting, and the struggle of balancing life with aging parents resonated.

Julie R. Gralow, MD

Chief medical officer, American Society of Clinical Oncology

- ***The Third Pole: Mystery, Obsession, and Death on Mount Everest***, by Mark Synnott
- ***Caste: The Origins of Our Discontents***, by Isabel Wilkerson
- ***Curse of the Pogo Stick*** (Dr. Siri Mysteries Book 5), by Colin Cotterill
- ***The Optimist: A Case for the Fly Fishing Life***, by David Coggins

- ***Mission To Space***, by John Herrington

The Third Pole: Mystery, Obsession and Death on Mount Everest: Having climbed to Everest Basecamp in 2017 with the non-profit Radiating Hope, I was intrigued by this account of the author's expedition in search of evidence that George Mallory and Sandy Irvine may have been the first to summit Mount Everest in 1924, well before Hillary and Norgay became the first confirmed to reach the summit in 1953.

While I have zero interest in the oxygen deprivation and danger associated with an actual Everest summit attempt, I do love the Himalayan mountains and people, and am enjoying experiencing this adventure, along with the mystery of Mallory and Irvine, through this book.

Caste: The Origins of Our Discontents by Isabel Wilkerson: This will also likely be on several others' reading lists, but even if so it is certainly worth repeating. Cliff Hudis sent this book to me when I assumed my Chief Medical Officer role at ASCO, emphasizing ASCO's commitment to Equity, Diversity, and Inclusion.

The book describes our social structure as an unrecognized caste system based on skin color, and how this arbitrary hierarchy continues to divide us and contributes to our current societal inequities. The book is timely, extremely well-written, and eye-opening for me—causing me to do a lot of deep thinking and re-examination of my own privilege, actions, and relationships.

Curse of the Pogo Stick (Dr. Siri Mysteries Book 5) by Colin Cotterill: I'm a big fan of mysteries, especially those set in locations I've enjoyed through my international travel. One of my favorite trips was a trip to Vientiane and Luang Prabang, Laos, with a few of the faculty attending the South East Asia Breast Cancer Symposium.

This fun series is set in late-1970s Laos, and features Dr. Siri Paiboun, the national coroner of Laos, who ends up in the middle of many murder investigations. I enjoy the characters and dialogue, and especially the weaving of the history, politics, and mysticism of Hmong culture into the plots.

The Optimist: A Case for the Fly Fishing Life by David Coggins: My husband and I are listening to this as an audio book when we're on long drives or out in the boat this summer. While he is the real fisherman in the family, I enjoy the serenity of being on the water, and I also have the local claim-to-fame of winning the 2019 San Juan Island coho salmon derby! Each chapter focuses on a specific place, fish, and skill. The book is entertaining and humorous, and shows how fly fishing can teach focus, inner calmness, and a connection to nature.

Mission To Space by John Herrington: This is actually a children's book, and I purchased it after meeting author John Herrington this summer. He's a member of the Chickasaw tribe and NASA astronaut who was the first indigenous person in space.

We met at a small airport in Montana while on a cross-country trip in our Cessna. My father was a Navy test pilot, and I've always been interested in planes and flying. In the book Herrington talks about his astronaut training and his mission to the International Space Station. I particularly love the picture of his eagle feather and flute floating inside the International Space Station, and the English-to-Chickasaw vocabulary list of space-related terms created by the tribe to explain concepts like astronaut ("above walker" - aba nowa) and space shuttle ("flying canoe" – piini wakaa).

Daniel F. Hayes, MD

The Stuart B. Padnos Professor of Breast Cancer Research, Professor of internal medicine, University Michigan Rogel Cancer Center

- ***Home Waters - A Chronicle of Family and a River***, by John N. Maclean

I am currently reading *Home Waters - A Chronicle of Family and a River* by John N. Maclean, the son of Norman Maclean, the author of *A River Runs Through It*, which was, as I'm sure you are aware, made into a movie starring Robert Redford and Brad Pitt.

I am an avid, although infrequent, fly fisherman, and so this book is particularly enjoyable. In it, Mr. Maclean chronicles the pioneering experience of his grandfather, a Presbyterian minister who moved his family (including Norman and his brother Paul) to Missoula Montana at the turn of the 20th century and their love of fly fishing.

He covers his own family's illustrious history, especially that of his father (who taught English and Literature at the University of Chicago but always returned to Montana for summer outings) and his Uncle Paul. You may recall that in the movie, Paul (played by Brad Pitt) is apparently murdered in Montana after an evening of drinking and gambling. In real life, he was murdered in Chicago under very mysterious circumstances.

He also provides insight into the original foray of Europeans into the area, famously highlighted by Merriweather Lewis's (of Lewis and Clark) brief separation from Clark as he and a small band made a side expedition through the region.

I am particularly reading this book at this time because, in addition to it just having caught my eye, I am planning a fishing trip to the Bitterroot in September, which runs south out of Missoula. Although much of this book revolves around the Blackfoot and Clearwater Rivers, they all converge in Missoula, so, indeed, I'll be on a *River that Runs Through It*.

Strongly recommended for anyone who fly fishes, and modestly recommended for those who are interested in either Norman's original novella or the movie. I suspect anyone without either of these two interests may find it a bit plodding, but still worth the descriptions of one of the most beautiful settings in North America.

Matthew G. Vander Heiden, MD, PhD

Director, Koch Institute for Integrative Cancer Research;
Associate professor of biology,
Member of the MIT Center for Precision Cancer Medicine,
Ludwig Center for Molecular Oncology,
Broad Institute of Harvard and MIT

- ***The Idea Factory: Bell Labs and the Great Age of American Innovation***, by Jon Gertner
- ***Great Expectations***, by Charles Dickens
- ***Three Body-Problem*** trilogy, by Cixin Liu

The Idea Factory is the story of Bell Labs, the research institute that was the source of an astounding amount of technological innovation in the 20th century.

This book resonated with me because it highlighted how important it is to give people creative license to do basic research, even when there is not a clear translational application or short term goal in mind.

This approach is becoming less common in today's research enterprise and we are increasingly losing sight of the importance of creative freedom in how we fund and reward research.

I read *Great Expectations* because my high school daughter was assigned it for school, and I realized that it was a classic novel that I had not read.

I really enjoyed this quintessential coming-of-age story, as it was a nice escape to enter Dickens's world and appreciate his keen observations of humans.

I read the *Three Body Problem* trilogy over the past couple of years and really appreciated this intelligent science fiction series. Liu is brilliant in working modern physical theories into an interesting story involving human contact with life elsewhere in the universe. This is also a series that gets better with each book.

Shikha Jain, MD

Assistant professor of medicine,
Division of Hematology and Oncology,
University of Illinois, Chicago;
Director of communications strategies in medicine,
Associate director of oncology communication and digital innovation,
University of Illinois Cancer Center

- ***When Breath Becomes Air***, by Paul Kalanithi
- ***Why So Slow? The Advancement of Women***, by Virgina Valian

Two books that I am currently reading that really resonate with me are the following:

In anticipation of our upcoming Women in Medicine Summit where Dr. Lucy Kalanithi will be one of our keynote speakers, I am re-reading the book written by her late husband Dr. Paul Kalanithi, *When Breath Becomes Air.* I could quote the entire book when sharing sections that stay with me. Here are the two I chose. The first is when Dr. Kalinithi's oncologist makes this powerful statement:

"I'm totally happy for us to make your medical plan together; obviously you're a doctor, you know what you're talking about, and it's your life. But if you ever want me to just be the doctor, I'm happy to do that too."

Different patients desire a different level of involvement in their own care. Some prefer a physician to make all their decisions, while others prefer a team based approach where decision making is done with physician and patient discussing and weighing the options together.

As a patient who is also a physician, the burden of trying to manage and understand one's own diagnosis, and make decisions based on what the science says, and what is in line with one's own personal goals and desires, can be a difficult internal struggle. Objectivity in taking care of the patient can go right out the window when the patient requiring treatment is you.

This statement from Dr. Kalanithi's oncologist is so powerful and so important. Sometimes, giving the patient the power to BE the patient by saying out loud these simple words, especially when the patient is in healthcare, can be exactly what they need to hear.

They may not want to abdicate that role, but giving them the choice to just be the patient may allow them to traverse the diagnosis with more peace of mind, regardless of the way they choose to move forward. And in the future, if they decide to just be the patent, mentally they have been given the permission to do just that.

Another section that sticks out comes from the epilogue:

"This book carries the urgency of racing against time, of having important things to say. Paul confronted death-examined it, wrestled with it, accepted it- as a physician and a patient. He wanted to help people understand death and face their mortality. Dying in one's fourth decade is unusual now, but dying is not."

As an oncologist, I walk patients through death and dying on a regular basis. Simply seeing a visit with me on their calendar can elicit high levels of anxiety and stress for my patients and their families. With each visit, phone call, conversation, my patients and their families worry if this will be the time I tell them the cancer has recurred, or if we have run out of treatment options.

That humanity, remembering that each person has a family, a job, a life, outside of the walls of our clinic, of our hospital, is what makes me more dedicated to providing each patient care personalized to their lives.

Allowing my patients to not just exist with cancer, but live with cancer, get the most of their time on earth and feel some control, when they often feel they have lost any decision making in their lives, that is what continues to drive me forward as an oncologist.

This book, and Drs. Paul and Lucy Kalinithi's story, is a beautiful, poignant, and sometimes painful reminder of what our patients experience when they leave the doors of our clinics.

I am also reading *Why So Slow? The Advancement of Women* by Virgina Valian.

Several sections in this book bring up questions and solutions posed in unique ways that I think get to the heart of why gender inequities are so pervasive in our society. One such example is this section:

"Two different questions can be posed. The first is, why have women advanced as much as they have? The second is, Why have they advanced so slowly? The second question is easier to answer than the first. Schemas change slowly, especially if people do not know how schemas operate. Even when they do know, they may require frequent reminders... Unless we- women and men alike- understand how gender schemas disadvantage women professionally, women will not receive the positive evaluations their work merits, women will get less than their fair share, and women's advancement will continue to be slow."

This book also provides some powerful solutions on how to work towards a more equitable society including more accurate evaluations, challenging our own underlying biases, conducting thought experiments by switching the sexes and seeing if your conclusions remain, awareness training, institutional policy changes, and more objective performance evaluation criteria, to name a few. Many of these types of interventions can all make an impact and are just a few of the solutions described in this objective, well-written, thoughtful scholarly book.

Walter Lawrence Jr., MD

Director emeritus,
Virginia Commonwealth University
Massey Cancer Center

- ***A Promised Land***, by Barack Obama

A Promised Land by Barack Obama is a very personal story from our young and very first black president that begins with a few details of his early days in my old home town (Chicago) with Michelle and then a small family, and how he was stung by the "bug" of politics and public office.

The excitement and stress of campaigning for the presidency as a young devoted family man, the vital roles of his team-mates through this and later endeavors and the challenges he felt in his role as "leader of the free world" really come through in this truly exciting account of a few short years of the author's life.

Merry-Jennifer Markham, MD

Chief and Professor,
University of Florida,
Division of Hematology & Oncology

- ***Project Hail Mary: A Novel***, by Andy Weir
- ***The House in the Cerulean Sea***, by T.J. Klune
- ***Set Me On Fire: A Poem for Every Feeling***, by Ella Risbridger

At any given time, I'm reading at least two books. I read one on my Kindle and the other I listen to on audio while driving. I prefer fiction of all types (except romance) but I've recently been exploring poetry. This is one habit I picked up at the beginning of the pandemic, and I'm grateful for it.

Project Hail Mary: A Novel by Andy Weir is science fiction at its absolute best. The plot involves a science teacher who finds himself on a space mission to save Earth, and the story is filled with science, mystery, and humor. Ultimately, it's a story about life and friendship, and I'm so sad I finished reading it.

The House in the Cerulean Sea is a lovely story about a man who finds family in a very unexpected place. This book is in the fantasy genre, and despite the fact that I don't like romance novels, this turns out to be a love story in the end. It's beautiful and heartwarming, and I found myself smiling the entire way through it.

Set Me On Fire: A Poem for Every Feeling is an anthology of poetry compiled by Ella Risbridger. She explains in her introduction and at the end of the book that she began writing the book for her best friend, who hated poetry, as a way of showing her what good poetry could be. And oh, does she succeed. The anthology is filled with a diversity of poems, written by a wonderfully diverse group of poets, and I highly recommend keeping this by your bed or on your living room coffee table so it's easily accessible.

Ruben A. Mesa, MD

Executive director,
Mays Family Foundation Distinguished University Presidential Chair,
Professor of medicine,
Mays Cancer Center,
UT Health San Antonio MD Anderson

- ***The Cellist***, by Daniel Silva

Nothing I enjoy more on my summer holiday than sitting by the cool waters of Lake Michigan with family and reading a fun book. I look to summer to recharge and read something unrelated to our shared cancer mission, and a chance to escape.

I look forward each year to the annual installment of the adventures of spymaster and master art restorer Gabriel Allon as wonderfully written by Daniel Silva. This year's installment, *The Cellist*, did not disappoint!

Adekunle Odunsi, MD, PhD

AbbVie Foundation Director,
University of Chicago Medicine Comprehensive Cancer Center;
AbbVie Foundation Distinguished Service Professor of Obstetrics and Gynecology,
Dean for oncology,
Biological Sciences Division,
UChicago Medicine

- ***Radical Candor: Fully Revised & Updated Edition: Be A Kick-Ass Boss Without Losing Your Humanity***, by Kim Scott

I am reading *Radical Candor: Fully Revised & Updated Edition: Be A Kick-Ass Boss Without Losing Your Humanity* by Kim Scott, CEO coach and former lead at a number of tech companies. This book is of interest as it explains different styles of leadership and how to utilize them to be an effective leader in the workplace.

Coral Olazagasti, MD

Hematology/oncology fellow,
Department of Medicine,
Division of Hematology-Oncology,
Zucker School of Medicine at Hofstra/
Northwell Health Cancer Institute

- ***A Thousand Splendid Suns***, by Khaled Hussein

I read to briefly escape my daily routine and anything related to medicine, especially during the past year where we have been consumed and overwhelmed by COVID. I like to lose myself in a story that not only does not resemble my current life, but also teaches me about history, current events, or other ways of living. *A Thousand Splendid Suns* details the beautiful story of two women from different generations that are subjected to an arranged marriage to the same man. During the novel, the women create a "mother-daughter-like bond" through similar shared experiences during Afghanistan's civil war.

Suresh S. Ramalingam, MD

Executive director, Winship
Cancer Institute,
Roberto C. Goizueta Chair
for Cancer Research,
Emory University School of Medicine

- ***Supreme Inequality: The Supreme Court's Fifty-Year Battle For A More Unjust America***, by Adam Cohen

I recently read the book *Supreme Inequality: The Supreme Court's Fifty-Year Battle For A More Unjust America* by Adam Cohen.

This book reviews the impact of the shift in the US Supreme Court in a conservative direction 50 years ago on major court rulings since. Cases decided by the court addressing several important topics including education, campaign finance, and criminal justice are described in length.

The author makes a compelling case to show that the interests of the common man have been left behind and this has made a huge impact on the present society. Given that the present composition of the court has turned even more conservative, it should be of concern to everyone as to where we are headed.

This book is sure to raise the reader's blood pressure, but hopefully will also increase one's commitment to speak up for the less fortunate.

Azra Raza, MD

Chan Soon-Shiong Professor of Medicine,
Director of the Myelodysplastic
Syndrome Center,
Columbia University;
Author, The First Cell: And the Human
Costs of Pursuing Cancer to the Last

- ***Swann's Way: In Search of Lost Time, Vol. 1***, by Marcel Proust, translated by Lydia Davis
- ***The Secret Sharer***, by Joseph Conrad
- ***The Making of the Atomic Bomb***, by Richard Rhodes

"How is it possible that you have not read Proust?" asked my friend Sharon Cameron, professor of English literature at Johns Hopkins. I had no excuse except to say I was daunted by the set of five volumes. "Order *Swann's Way* translated by Lydia Davis immediately." I did. I am into volume three presently. Completely ravished.

Others have commented on the musicality of Proust's language, the attention he pays to the minutiae of detail concerning the smallest observation, every perception, his exquisite sensibility and sensitivity.

For me, he reigns supreme when writing about love. In Toni Morrison's BELOVED, when Paul D tells Sethe, "Girl your love too thick," she responds, "Love ain't thick or thin. It either is or ain't." It is so with Proust. And does he know how to describe both states—the utter madness, the blinding passion, the consuming insanity of falling in love, as well as the disheartening, disillusioning, sorry disenchantment of falling out. I am smitten forever and will read and reread Proust for the rest of my life, even if just for the experiential delight of his glorious writing.

COVID-19 lockdown provided an exceptional opportunity for reading. Obsessed by the question of how a normal cell transforms itself into a malignant killing machine bent upon destroying its very creator, I spent the year reviewing everything there is to know about the phases The First Cell in statu nascendi must transition through.

At the same time, as I was mulling over the idea that The First Cell may be two cells, I read Joseph Conrad's *The Secret Sharer*. Conrad explores the needs of concealment in both the Captain of a Ship whose cabin is parasitized by a crafty, deadly killer, and the need of the murderer to hide while coming to terms with his rageful impulses leading to the accidental death of a shipmate. And suddenly I could imagine how a stressed malignant cell could also worm its way into a normal blood cell and become the secret sharer of its passport to travel all over the body in search of new homes, hiding in plain sight, while the normal cell is forced to conceal the secret sharer because of the potential for immortality it brings along. Give up the secret sharer and the blood cell will age and die. Fiction supplements imagination.

Another book I should have read a long time ago but got to this fall because it arrived as a birthday present from my brother Abbas. Published in 1986, simply magnificent in scope, written in noble language, exceptionally gripping in its powers of story-telling, *The Making of the Atomic Bomb* remains startlingly relevant today. Rhodes starts with the birth of the atom and quantum physics providing splendid biographies of the men and women involved, making them come alive.

From the tragic rise of anti-Semitism and Fascism to the eruption of the second World War, he recounts extraordinary acts of heroism and extreme cruelty by leaders on the world's stage, the firebombing that razed thriving cities into ash overnight, the stunning show of patriotism and resistance by the Japanese forcing the gruesome solution in Hiroshima.

It is at least ten books in one. It has become, very simply, the best book about science I have ever read.

Vanessa Sheppard, PhD

Professor and chair, Department of Health Behavior and Policy, Theresa A. Thomas Memorial Chair in Cancer Prevention and Control; Associate center director, Community outreach engagement and health disparities, Virginia Commonwealth University Massey Cancer Center

- ***The Other Einstein***, by Marie Benedict
- ***Four Hundred Souls: A Community History of African America, 1619-2019***, edited by Ibram X. Kendi and Keisha N. Blain

The Other Einstein by Marie Benedict: In this book, I met Mitza Maric who is described as being "a little different from other girls". Thankfully, we now celebrate and encourage this "difference". I enjoy obtaining insight into the social and political context of pioneer female scientists. Peering into the heart and mind of Einstein's first wife and her love of science (and him) was intriguing, entertaining and a great summer read!

Four Hundred Souls: A Community History of African America, 1619-2019: This communal diary was penned when African America symbolically turned 400 years old. It is an innovative, moving, poetic and passionate collective. Rather than "reading" this community history, I have been slowing digesting and savoring every morsel of the masterfully written prose.

The taste may be too bitter for some as we often too quickly summarize the ills of enslavement. I have re-read sections, underlined facts, read aloud to my family and experienced this book. *400 Souls* stirred emotions of anger, sadness, pride, and jubilance.

As a history enthusiast, I wondered how the field trips of my childhood would have been different if at least some of the history unearthed in *400 Souls* would have been shared.

The book is filled with stories of struggle and resilience and the connections to our contemporary life are clear. It reminds us that racism is not unique to America and chronicles the development of legislation, religious practices, and policies that birthed a complex structure of anti-Black racism.

I was moved to learn about Elizabeth Keye, an African American woman who during the colonial period instigated the "single most important legislative acting concern the history of enslavement, race, and reproduction in the colonial Atlantic world" (pg 39). It is a must read for all who live in America—particularly those who are committed to eradicating suffering from cancer and other diseases.

Living and working in the symbolic birthplace of African America, I am recharged to contribute towards the dismantling of structural racism.

John Stewart, MD, MBA

Associate director for clinical research, Department of Surgery, College of Medicine, Full member, Translational Oncology Program, University of Illinois Cancer Center

- ***I Came As A Shadow: An Autobiography***, by John Thompson with Jesse Washington

I have read several books this summer, but my favorite was *I Came As A Shadow: An Autobiography* by John Thompson with Jesse Washington.

> I came as a shadow,
> I stand now in light;
> The depth of my darkness
> Transfigures the light.
> -Lewis Grandison Alexander

Coach John Thompson was an iconic NCAA championship coach, educator, and social activist. *I Came as a Shadow* details the many influences that shaped John Thompson. These early influences informed Coach Thompson's views on many controversial topics including his protest of Proposition 42 which would have denied many players the opportunity to become student-athletes.

John Thompson was more than a coach, he was a molder and leader of men. His off the court mentorship shaped the lives of many players including Allen Iverson, Dikembe Mutombo, Alonzo Mourning, and Patrick Ewing. Perhaps Coach Thompson's relationship with Georgetown can be best summarized by the quote that is engraved on his statue in the John Thompson Athletic Center, "When I'm gone, if I can't go to Heaven, take me back to Georgetown."

Ishwaria Subbiah, MD, MS

Palliative care physician, Medical oncologist, Department of Palliative, Rehabilitation, and Integrative Medicine, Division of Cancer Medicine, MD Anderson Cancer Center

- ***Mad Scenes and Exit Arias: The Death of the New York City Opera and the Future of Opera in America***, by Heidi Waleson
- **WorkLife with Adam Grant: a TED original podcast**

Mad Scenes and Exit Arias: The Death of the New York City Opera and the Future of Opera in America by Heidi Waleson—A sizable proportion of ideas and inspiration, I find outside of the healthcare environment. Understanding upheaval, reconciling with change, and observing organizations riding the realities around them are hardly unique to healthcare.

Though I've had the book on my shelf for about two years, I just recently picked up and finished Heidi Waleson's *Mad Scenes and Exit Arias: The Death of the New York City Opera and the Future of Opera in America*. The content centers around the collapse of an institution built on a noble charge of providing accessibility to a cloistered entity (in this case, opera) to a broader community.

Ms. Waleson, who is the opera critic for the Wall Street Journal for over two decades, expertly describes the circumstances of this organization—you see the decision-making over the years leading up to the unfortunate final outcome and, more importantly, you recognize the interplay between one organization, a wavering strategic vision, and an equally flawed implementation strategy, all occurring in an environment with overwhelming external forces impacting (nay, interfering) with its existence. Learning from history is a privilege for those who choose to do so—this book provides that type of insight.

WorkLife with Adam Grant: a TED original podcast—My absolute favorite group of academics are industrial-organizational (IO) psychologists—as a field, IO psychology provides a clarity into the workplace experience that is based on rigorous quantitative research and evaluation methodology. Adam Grant, an organizational psychologist at Penn, has a very engaging TED original podcast called WorkLife with Adam Grant.

I listen to episodes on my runs but then when I'm stationary (in the evening or on flights), I relisten and follow along with the transcript online because he links out to the original research studies that he references in those conversations. Each episode is concise and topic-focused with guests who often played key roles in events of global consequence.

The real fun is when you go down the rabbit hole and read more into the linked studies and into the work of his guests. A must-listen episode is How to Rethink a Bad Decision, which provided me with an eye-opening understanding of sunk costs – the linked study was a fascinating meta-analysis on the project, psychological, social, and structural determinants that impact the escalation of commitment into a proverbial lost cause.

This content will likely resonate with many in clinical oncology as we collectively look to reclaim ownership of our own and our team's time and to raise the level of self-awareness in the workplace.

Robert Vonderheide, MD, DPhil

Director, John H. Glick Abramson
Cancer Center Professor,
Abramson Cancer Center;
Vice dean and vice president
of cancer programs,
Perelman School of Medicine
and University of Pennsylvania
Health System,
University of Pennsylvania

- ***A Promised Land***. by Barack Obama
- ***Eat A Peach: A Memoir***, by David Chang

Each of the last two books I have read this summer are memoirs, both interesting takes on strategy and messaging in the face of big leaps.

Obama's *A Promised Land* reveals the balance a leader faces trying to carefully craft values-driven policy vs. being ready when chance opportunities arise. The self-told story of designing and passing the Affordable Care Act is most interesting. The anecdotes are informative too: I personally can't hear the "Fired Up – Ready to Go" campaign story too many times.

Obama describes his efforts not to be so long-winded in a bumper-sticker world, but there's still apparently a learning curve because these 701 pages only get the story to half way through his first term!

David Chang's *Eat A Peach* is from the now celebrity chef who started Momofuku Noodle Bar in Manhattan nearly 20 years ago. The tale moves pretty fast and is told quite casually, but there are definitely pauses here for leadership lessons that go beyond the restaurant industry, such as Don't serve dumplings just because you think you should. And perhaps more important: Don't assume that your clever, made-up, fast-food Korean burritos will be a hit either.

Karriem S. Watson, DHS, MS, MPH

Associate executive director,
Mile Square Health Center FQHCs;
Associate director,
Community outreach and engagement,
University of Illinois Cancer Center

- ***Caste: The Origins of Our Discontents***, by Isabel Wilkerson
- ***The Big Leap: Conquer Your Hidden Fear and Take Life to the Next Level***, by Gay Hendricks

I am reading the second work of Isabela Wilkinson that provides an in-depth look into how we think about the Caste system in the US. As we explore precision and individualized medicine, this work reminds us to explore those factors beyond race but to do an examination of how and why people are "grouped" in our culture and how those groupings can inform health and other life outcomes.

The Big Leap is a book that was recommended to me by a friend and life coach. The book takes the reader through some real introspection of life's barriers that may be preventing us from going from good to great. It provides the reader with real life tools on how to remove those obstacles that either we or life has placed in front of us that prevents us from living our best life.

BOOK REVIEW

Books that mattered to me this year

Over the past year, I noticed several books written by giants in our field, people everyone knows, people I am honored to know personally. I was interested in what they wrote, and I thought their books would be of general interest to *The Cancer Letter* community.

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Going beyond merely recommending the books, I set out to write in a book review format, providing critiques that would enable everyone to appreciate more of the details (and want to read the books).

Because of my interest (or because I know the subject matter and, in some cases, am acquainted with the authors), I included reflections on the aspects of the books I found interesting, adding perspective or insight when appropriate.

You will find a lot of interesting history and fascinating tidbits within these volumes—including the personal human side of science and medicine. Perhaps I got a little carried away with the number of words, but I wanted to do these books justice. I know my colleagues will be eager to read every word. And maybe some will be inspired to do similar things—maybe we could start something new here.

Perhaps it was an unusual year for those types of books that I gravitated toward. Rather than sticking with my typical diet of sci-fi, social justice, history, and entertainment, I gravitated toward important and timely social and ethical issues in science and oncology.

I hope the reader gets all the way down to the bottom of the list (especially the book my daughter Julie is reading), and, finally, I wish there were more hours in the day.

The books reviewed here are:

- *What is Life? Five Great Ideas in Biology*, by Paul Nurse
- *Guinea-Pig Doctors: The Drama of Medical Research Through Self-Experimentation*, by Jon Franklin and Jon Sutherland (out of print)
- *Letter To A Young Female Physician: Notes from a Medical Life*, by Suzanne Koven
- *Off Our Chests: A Candid Tour Through The World Of Cancer*, by John Marshall and Liza Marshall
- *Editing Humanity: The CRISPR Revolution And The New Era Of Genome Editing*, by Kevin Davies
- *100 Questions and Answers About Ovarian Cancer, 4th Edition*, by Don Dizon, Dorinda "Dee" Sparacio, and Vance Broach
- *Rethinking Cancer: A New Paradigm for the Post-Genomic Era*, by Bernhard Strauss, Marta Bertolaso, Ingemar Ernberg, and Minna J. Bissell

Other books on my reading list are:

- *Why Fish Don't Exist: A Story Of Loss, Love, And The Hidden Order Of Life*, by Lulu Miller
- *The Black Swan*, by Nassim Nicholas Taleb

And a book my daughter, Julie, is reading:

- *Heartland: A Memoir of Working Hard and Being Broke in the Richest Country on Earth*, by Sarah Smarsh

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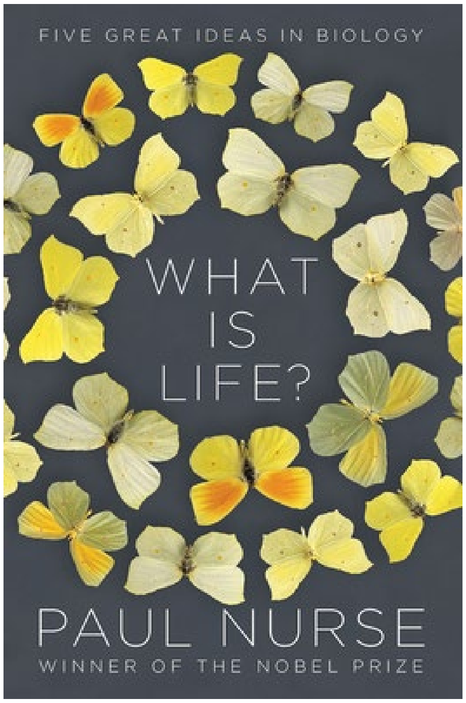
What is Life? Five Great Ideas in Biology



When a Nobel Laureate like Paul Nurse stops to ask what it means to be alive or what defines life, one can be sure that something interesting and important will be learned.

The basic unit of matter is the atom. The basic unit of life (the first step), the cell varies widely in size, for example 3,000 bacteria add up to a mm, while a single nerve cell from the spine to the big toe can be a meter long. Virchow '*Omnis cellula e cellula*', or "all cells come from other cells," is pretty profound.

We all were single embryonic cells; life does not ordinarily arise from inert matter. At the core of cells are the genes, and their history dates back to before it was known what genes were. Gregor Mendel studied inheritance patterns in pea plants and referred to pairs of 'elements' and specific patterns he observed were later understood to apply to all sexually reproducing species. Microscopy was used by Anton van Leeuwenhoek, and later by Matthias Schleiden and Theodore Schwann in the late 1830's to observe cells.

By the 1870s, Walther Flemming observed 'threads' in cells that separated as cells divided, later called chromosomes, physical manifestations of genes, the heritable particles proposed by Mendel. While it became known that chromosomes contained deoxyribonucleic acids, work of Oswald Avery in the early 1940's, "most biologists thought that DNA was too simple and boring a molecule to be responsible for such a complex phenomenon as heredity."

Nurse recounts how the structure of DNA was transformational as were its implications for heredity. The gene is the second step in understanding the biology of life. He got to know Watson and Crick and describes how they were and how they complemented each other.

The genetic code was broken in the late 1960s and early 1970s. Nurse describes Sydney Brenner as having interviewed him for a job he didn't get, during which he compared his colleagues "to the crazed figures in Picasso's painting Guernica, which hung on the wall of his office."

Genetically modified bacteria were developed by the late 1970s and instructed to produce insulin, while Fred Sanger worked out methods to sequence DNA, and the human genome was sequenced by 2003. Nurse goes into how the control of mitosis and the cell cycle to ensure faithful replication and cell division is what makes life possible for a cell. He recounts laborious work with yeast mutants that led him to identify the small 'wee' mutants, at least 50 of them, and then the cdc2 mutant that unlocked a fundamental mechanism of cell division.

Nurse recounts a personal story about his own genetics with shocking revelations for him as he was moving to become president of Rockefeller University. You'll have to read his book for that information.

The book turns to evolution, natural selection as an important feature of life (the third step), ideas of Lamarck and (Charles) Darwin (and his grandfather Erasmus who was also a doctor and poet). He mentioned others before them and also described the influence of artificial selection used by humans, such as breeding pigeons or dogs, on directed evolution.

Even the error rate of DNA replication is subject to natural selection. Nurse describes life on our planet as all connected, and recounts an experience on a visit to Africa with a gorilla and then the amazing conservation in cell cycle control between yeast and human cells, at least as far as cdc2.

It is interesting to me, that four decades after its discovery, there has not been a description of a yeast p53 homologue or a cell cycle checkpoint mechanism like p53 activation of the mammalian CDK inhibitor p21(WAF1)/CDKN1A, one of my most favorite genes that mediates growth arrest to allow DNA repair in damaged or stressed cells.

Nurse gets into another (the fourth step) aspect of life through chemistry and chemical reactions. He describes insights by Pasteur that 'chemical reactions are expressions of the life of the cell'. "Metabolism is the chemistry of life" is something that many cancer researchers in 2021 are focused on.

He points out that enzymes are catalysts that support life. The compartmentalization within cells is viewed as a way that a vast array of chemical and metabolic reactions can occur to sustain life. Life is also powered by ATP made in mitochondria. Finally, Nurse describes a key aspect of life (the fifth step) as information, sensing, responding and adapting, and posits that purposeful behavior is a defining feature of life.

The book discusses much more about the organization and regulation that makes life possible. Nurse includes a chapter about changing the world with new ideas and technologies, and how the world has changed as a result of all the progress that has been made through science. He ends the book with his approach to defining life by providing essential principles that build upon the five steps, recounts ideas of others, and offers some of his own speculation about the origin of life.

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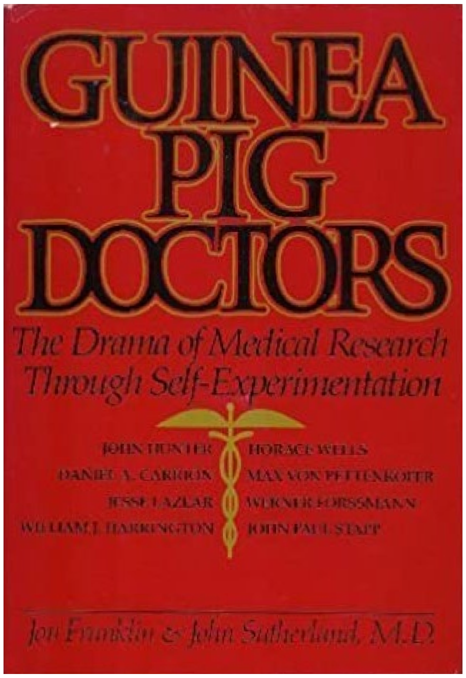
Guinea-Pig Doctors: The Drama of Medical Research Through Self-Experimentation



I read this book while in medical school, but became interested in it this past year, as I think it brings back a history of medicine and a kind of explorer who has been lost in the modern era.

If bureaucratic heads would roll in Washington, the answer from the FDA would have to be "no" as far as starting human studies with thymidine as a cancer therapeutic without preclinical evidence of safety.

Thus, Dr. Beppino Giovanella wrote a clinical protocol for himself, and took thymidine orally in increasing doses. He developed diarrhea and couldn't absorb enough to reach high blood levels. So, he injected himself with IV thymidine and went to the FDA with evidence of safety and they reversed their decision to allow clinical testing in patients with terminal cancer. But not all chemotherapy works…

Dr. Horace Wells, a dentist and inventor in Hartford, CT, was successful but felt his profession was unpleasant because of the pain his patients had to endure. He observed a demonstration of the effect of laughing gas when a circus performer hurt himself and felt no pain. He set up a demonstration on himself of what would be a painless tooth extraction.

His demonstration in Boston to the Harvard surgeons didn't go smoothly because of his nervousness and their arrogant skepticism. He abandoned dentistry but was urged by his family to patent the nitrous oxide gas.

He wouldn't give his former student Morton, in Boston, the gas, and Morton eventually experimented with ether, also being talked about at the time, on his dog and goldfish. Morton eventually made a demonstration for the surgeons at Harvard and it went well for the removal of a neck tumor painlessly.

The story gets interesting with disputes in 1846 between Wells, Morton, and Jackson each claiming they made the invention. Desperation, anguish, and madness are part of this story and eventually credit for the discovery of anesthesia is settled but not before a human toll is taken. Read about it to find out what happened.

Several other guinea pig doctor stories are included about cholera, yellow fever, tubes inside the body—whether it's the heart or kidneys combined with X-rays, to push back the frontiers of medicine. One story I read in the 1980s is about Dr. William J. Harrington, who was chair of medicine at University of Miami, who was also head of hematology and on the faculty while I was a student there.

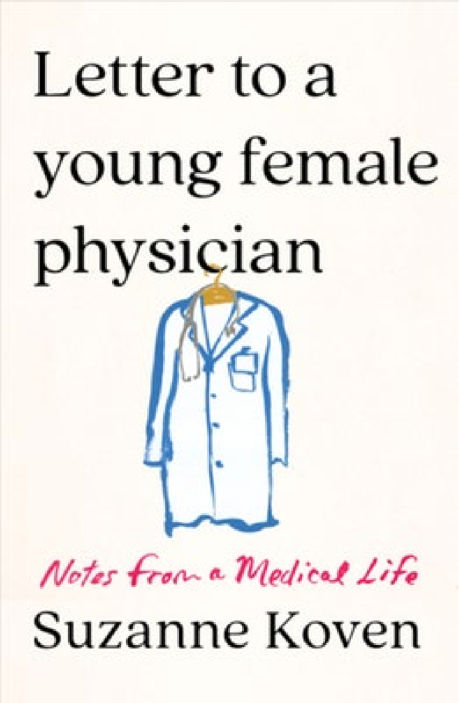
I met him at the end of my hematology rotation and remember, to this day, that when examined by a hematologist, one should always have in the back of their mind that the answer might be to do a bone marrow examination.

Dr. Harrington had met a young patient who was bleeding when he was a medical student in Boston. His patient had no platelets and died from surgery to remove her spleen. Later, as a hematology fellow at Barnes Jewish Hospital in St. Louis, he would inject himself with a pint of blood from a patient with severe ITP who had not improved despite a splenectomy.

Bill's own platelet count went down to zero for 5 days and he had bleeding around his ankles and in his stools. He had multiple blood and bone marrow examinations during the days that followed until his platelets recovered. His self-experimentation was the first example of a demonstration of autoimmune disease.

Interestingly, the book recounts that other staff members, secretaries, medical students and physicians in the summer and Fall of 1950 participated in similar experimentation with transfusions under more controlled settings. Dr. Harrington presented his paper at the 43rd annual meeting of the American Society for Clinical Investigation.

Letter To A Young Female Physician: Notes from a Medical Life



It was quite a treat for me to read this book, as I had met Dr. [Suzanne] Koven during medicine house-staff training at Johns Hopkins, and in fact she was my chief resident ("the third woman in the department's hundred-year history and the only married woman or woman with a baby to be selected for this honor.") during my senior medical resident year.

Dr. Koven, who was an English major in college, and had wanted to become a journalist, has an incredible talent for writing and flowery language. She recounts her journey with a special kind of humor. "The only thing I remember from my introductory chemistry course is that Einstein calculated Avogadro's number (6.022 x 1023) using grains of pollen. I never understood what Avogadro's number was, but I enjoyed picturing the wild-haired genius with his loupe and tweezers painstakingly dissecting the sex organs of flowers."

The "Letter" she wrote to a young female physician is about what to expect in a male-dominated medical world, with many challenges from "sexism, some infuriating, some merely annoying," "serious and damaging discrimination," "imposter syndrome" and ends with recognition of a mature "state of humility," and self-reflection for the benefit of her younger colleagues.

She quotes Sir William Osler: "There are three classes of human beings: men, women, and women physicians."

Koven admits her "complicity in a system that had so little regard for me," and states "perhaps the reason I didn't rebel against the culture of my medical training was that I loved it."

Dr. Koven writes about her father who was an orthopedic surgeon with whom she spent time in the office after school.

"What I wanted, I think, during those afternoons when I dipped x-rays into vats of sharp-smelling chemicals and held down limbs as the circular saw screeched through plaster casts, was to be close to my father, about whom I was endlessly curious."

On why she didn't become a psychiatrist, which she considered at one time, she mentioned a joke her father, the surgeon, told her "The internist knows everything and does nothing, the surgeon knows nothing and does everything, the psychiatrist knows nothing and does nothing, and the pathologist knows everything and does everything a day too late."

She writes in a chapter entitled "Things shameful to be spoken about:" "I've always been a talker. Mrs. Sylvia Krensky wrote on my otherwise unblemished first-grade report card: *Suzanne must learn to let the other children speak*. I never did. To this day I'm a chronic interrupter and conversation hog."

In her book, Dr. Koven shares much about her personal life through various transitions and some of what she went through, with wisdom, knowledge and poetry interspersed.

In her own words, she shares her tribulations, "the idea that I'd misdiagnosed my mother due to my incompetence was too painful for me to dwell on for too long. I quickly moved on to another theory: that my mother's diagnosis had eluded me for the same reason it had eluded her internist in Florida during the many months she'd complained to him about fatigue and left-shoulder pain; she was a woman."

Dr. Koven recounts meeting a patient with leukemia during her clinical skills training as a medical student at Johns Hopkins. Her interview at that point captures when the patient's illness became apparent, during an afternoon when he was coaching his grandson's baseball team and suddenly became light-headed.

He "held on to the chain-link fence to keep from falling and as he looked at his fingers, wrapped tightly through the metal wire, he noticed how pale they were."

Months later, on an inpatient rotation when the patient was much sicker when she reviewed the notes from her earlier encounter "I tossed my old note back in the folder with my essays on *Black House* and *Mrs. Dalloway*, having concluded that it was, like they were, useless."

Then, she wrote this sentence that resonates a bit in the modern era of sometimes fragmented and impersonal medicine (although probably not the intended takeaway): "Then I wrote my new note as if I'd never met Mr. Blake before, as if I'd never heard his story."

Dr. Koven wrote a chapter about '*Mnemonics*,' that every medical student will appreciate. She tells her friend, another English major she had met at Yale: "'The pancreas!' I cried. 'I don't understand the pancreas!'"

In a chapter entitled "We Have a Body," Dr. Koven describes an experience with a patient with terminal ovarian cancer on a rotation at the old Baltimore City Hospital. You'll have to read the book, but Dr. Koven's compassion and the art of medicine come to mind as she looked into the patient's social history (a good thing for any doctor to do to understand more about their patient as a person) and what she did "to spend time at the bedside."

> “Dr. Koven's book has much more, and every medical student and doctor should read it. It recounts a history important for anyone interested in social justice in the medical field as well as addressing sexism in medicine.”

She reflects on her first experience with death. "It seems preposterous to me now, as a mother and as a doctor, that any responsible adult thought it was a good idea for our AP biology class to take a field trip to the Medical Examiner's Office of the City of New York to witness the autopsy of a nursing student from the Bronx who'd been stabbed to death the night before by her boyfriend."

She says this, among other things about her experience in anatomy. "At the end of the course there was no memorial service, there were no candles, no songs, and no prayers of gratitude, as there often are in medical schools today, to honor the people our bodies had once been."

Dr. Koven also addresses racism drawn from her experiences at Johns Hopkins.

"Dr. Taussig pointed to the blood bank and stated aloud what everyone knew: that the blood of Black people and the blood of white people were stored separately there." She then asked Henry (one of Dr. Koven's mentors who told her the story): "'Doesn't this strike you as very wrong?'"

Pediatric cardiologist Dr. Helen Taussig invented the "blue baby operation" known as the Blalock-Taussig, shunt and which should really be called the Blalock-Thomas-Taussig shunt in recognition of "Blalock's lab technician, a black man named Vivien Thomas, the grandson of a slave, who played a key role in perfecting the procedure."

Reading further about Dr. Koven's experiences and reflections, I thought she would have made an exceptionally great oncologist incorporating extensive clinical expertise and perhaps her own special impact on the field of palliative care to help patients. Who knows, maybe there would have even been a "Koven's syndrome."

In a chapter about "Lineage," Dr. Koven says "My true lineage, I now think, included Blackwell and Haseltine—not to mention Oprah, and my mother—at least as much as Osler." *The House of God* comes up a few times, along with “a novel called *Woman Doctor* written by Dr. Florence Haseltine with English professor Yvonne Yaw, at around the same time as Samuel Shem’s bestseller.

“Unlike *The House of God*, though, no one’s heard of *Woman Doctor*. It’s out of print. My copy has a tacky 70’s cover featuring a grainy photograph of a glamorous, dark-eyed, long-lashed woman in full surgical garb who looks nothing like Dr. Haseltine as she appears in her author photo.”

I was able to find a copy of Woman Doctor that I bought on Amazon, $6.55 Hardcover (for some reason, the paperback is listed from $38.50 and “Mass Market Paperback” $902.81).

Dr. Koven’s book has much more, and every medical student and doctor should read it. It recounts a history important for anyone interested in social justice in the medical field as well as addressing sexism in medicine. It is a classic by a masterful author who is a complex individual with very important messages and legacy. Her Letter to a Young Female Physician book is already a best seller.

On a personal note, by 1989, when Dr. Koven was my chief resident, she had encyclopedic knowledge of medicine, the poise and equanimity that the ‘Osler Marines’ aspire to and never appeared as an imposter per personal observations.

It is hard to know why we remember certain things, but I do recall a scene one morning on our Osler rounds where our team had an admission on Halstead 5, the famous step-down cardiology floor at Johns Hopkins.

As we were outside a patient’s room discussing the case, the patient’s heart stopped and they needed immediate resuscitation. Dr. Koven, chief resident and medical attending of record, very calmly picked up the paddles, and then passed them on to another team member to perform the electrical cardioversion. This was when she was fairly late in her pregnancy but functioning very admirably as our leader. As she handed the paddles off she had a smile or more of a smirk that all who know her would recognize, and then she said “perhaps someone else should do this.”

This was an intense time during residency training in an era without work-hour rules, or balance between learning and service. There were other memories and even conflicts, mostly suppressed but not all forgotten.

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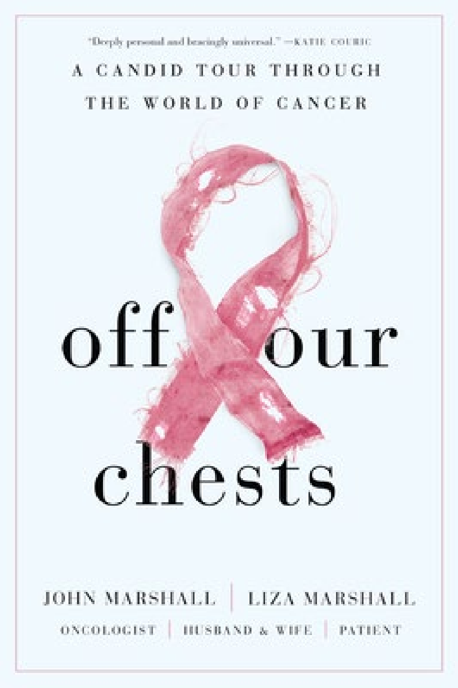
Off Our Chests: A Candid Tour Through The World Of Cancer



My colleague, John Marshall, who leads the Division of Hematology-Oncology, is a leader in our field, articulate, and well-known for his sense of humor. He directs the Otto Ruesch Center for the Cure of GI Cancer along with his wife Liza, who is a survivor of breast cancer. In this book, published in 2021, John and Liza share personal stories—and we can be grateful they shared them.

John begins the first part of the book entitled “Hail to the Queen” (referring to breast cancer as “the queen of all cancers”) by giving his perspective early in his career “I quickly came to see the ubiquitous pink ribbons as the enemy, a symbol of unfair focus in our field. Breast cancer comes first, and the rest of us get the leftovers…I preached my gospel of resentment and jealousy of breast cancer to anyone who would listen.”

He would say things in lectures such as “what color is the colon cancer ribbon? Come on, you in front? Brown? God, I wish it were a brown ribbon…” (and the comments went downhill from there, not to be repeated here).

He reminds the readers about how the Department of Defense came to fund breast cancer research, and how politically incorrect it would be to cut it even though it doesn’t kill most of those in the military. He felt an injustice towards the high mortality of some of the many patients he saw, including young people, with advanced GI cancers.

He says other funny things, like, “hematologists are full of themselves, a bit like peacocks” or “GI oncologists are the Gryffindors of the cancer world. We are by far the best humans God ever created…” His resentment was not helped when Georgetown recruited Marc Lippman as Cancer Center Director, and where “breast cancer ruled.”

Some chapters are written by John, and others by Liza. Liza found out she had breast cancer when a colleague of John’s walked into his office to share results of Liza’s breast tissue pathology that showed cancer cells in the lymph system, and Liza was on the phone speaking with him.

This was no joke. Liza’s previous experience with a close friend Holly in her mid-40's had shown the aggressiveness and deadliness of breast cancer a few years earlier. For Liza, John intervened to help her get scans quickly and even chipped in by showing up to a school activity so she could get away.

John had a difficult time in his teenage years with his mother's cancer and family's financial downturn. As he excelled in school, he would often hear from his dad, "If a boy like you doesn't succeed, who will?"

He recounts his spiritual life as a Baptist, and how with singing in the choir and other public speaking opportunities, he discovered his love of an audience and entertaining others. He lost his mom from Non-Hodgkin's Lymphoma before she was 40, when he was 13.

His father remarried, he went to boarding school and then to Duke University. Without much structure, he faced a low point in his life until he met Liza, then went to med school while she went to law school.

Liza recounts the testing she had with scans and how she and John handled telling their family, especially their children and other friends about the breast cancer diagnosis. Liza had to deal with hearing the diagnosis of "triple negative breast cancer," and that while cancer was seen in the lymphatic system in a core needle biopsy, the doctors didn't know where the primary tumor was and couldn't see it on her scans.

Liza would hear about the need for mastectomy surgery, chemotherapy, radiation, prosthetic breast, and the prospects of lymphedema. There were many options that were overwhelming, and some options that weren't discussed with Liza that she wished were discussed. The existing friendships made the doctor-patient relationships more complicated. John recounts what he observed, knew, wished he could say but didn't, how he remembers telling Liza, and his transition from physician to caregiver for Liza.

> He says other funny things, like, "hematologists are full of themselves, a bit like peacocks" or "GI oncologists are the Gryffindors of the cancer world. We are by far the best humans God ever created..."

John lectures about cancer and how it develops. He included a lecture from 2010 where he spoke about cancer vaccines as an area of interest, including combining vaccines and how NIH grant reviewers rejected his grant three times suggesting nothing would come of the research. In his lecture he said "Our microbiome is part of us—it might actually be the location of our souls." Profound statement, and then he suggested in 2010 that if NCI wouldn't fund vaccine research, they certainly wouldn't fund research on poop. He discusses diet and cancer and the "why me" question in his lecture.

It is interesting to read what John says: "Wherever two or more are gathered, I cannot keep my mouth shut. If an idea pops into my head, I express it. I have gotten better at not stepping in when others are talking, but I'm not perfect even with significant effort."

Here, he was referring to experiences with Liza's doctors. For those of us who know and work with John in national oncology activities, he is actually a great leader and expert moderator of discussion; one of the best I've seen (and not 'mansplaining' despite what he says).

He says it is easier for him to make decisions about what's best for him than what's best for someone else. Maybe, although it is easier to be objective when trying to help others. In academia, I've found it much easier to help others with their grants than to help myself.

For medical decisions, it can be very difficult in the middle of the storm to know what's best, and the input of others can be incredibly helpful. At the time Liza needed to make her decisions in 2006, less was known about triple negative breast cancer, and while a clinical trial of neoadjuvant therapy (chemotherapy before surgery, now standard of care for her case) was available, there was concern about waiting—and so she went ahead with surgery because surgery would happen either way. Within the chapters, both John and Liza discuss issues of intimacy and sexuality in the setting of mastectomy and breast cancer.

Liza recounts her surgery, more revelations about her diagnosis, and the experience of being at a teaching hospital, her admiration of George Clooney, more about the post-op period and their life together.

John writes about some of what happens to people in real life as cancer gets diagnosed at inopportune moments. He goes into oncology healthcare delivery, successes as a physician, realities and disappointments in medicine, competitiveness and the business of medicine, among other topics.

John declined the special invitation to attend the breast tumor board when Liza's case was being discussed. He spoke about how he started looking at patients differently when he sees them in the hospital every day, and how the experiences have affected how he does his job.

Liza describes learning about the pathology from her surgery, what others knew it meant, and complicated options in clinical trials for what would happen next. She goes into how and why John, who certainly knew much more, didn't necessarily say much beyond answering all her questions.

John recounts his struggles and reactions to Liza's illness as he became caregiver. For reasons he couldn't explain, he found himself not looking into details of the SWOG trial, the scans and pathology reports, asking a lot of questions, or attending lectures on TNBC even if pizza was served!

John presented a lecture about "finding value in cancer care," where he discussed healthcare economics and drug company profits from U.S. taxpayer funded research. He discussed red cell growth factors that he administered to Liza and information from trials that showed adverse outcomes.

He goes into dilemmas of being in the middle of an illness where you want to do everything no matter the cost, and value in healthcare, where ultimately, we as a society all pay the bills. The book goes into issues important for patients with breast cancer and their caregivers. The impact of a cancer diagnosis, especially one with a poor prognosis, and how it affects a family are discussed. Giving a shot of Neulasta even for an experienced physician is complicated if you don't let it warm to room temperature, don't give the shot slowly, and don't read the instructions.

One chapter I particularly appreciated was one John wrote about his perspective on funerals as an oncologist, and how he handles communications with family and caregivers after the death of a patient.

He tells a story at Holly's funeral, where an elderly U.S. senator passed out (how he dealt with it, and how the balance of power in the U.S. Senate was changed for a moment) and recounts his first experience with a cancer funeral at the age of 13 when his mother died.

He speaks about how he personally handles the loss when a patient dies. John writes about how oncologists maintain hope, spin their message, think about quality of life, statistics, and clinical trials. He speaks about his interactions with colleagues after "going public." He goes into a cryptic message from Marc Lipmann (who had left Georgetown for the University of Michigan at that time) "your wife needs a platinum, Marc," and other discourse with Neil Love.

This is followed by a chapter entitled "Platinum, but not the pretty kind." Liza thinks Marc Lippman's message may have saved her life. There is more so take time to read, enjoy, and learn from this book.

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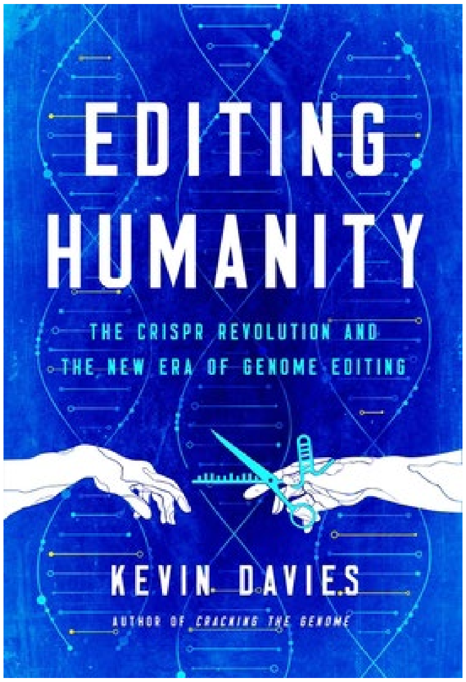
Editing Humanity: The CRISPR Revolution And The New Era Of Genome Editing



I was excited to see this book about the CRISPR revolution written by Kevin Davies. I first heard of Kevin Davies in 1992 during my postdoctoral fellowship, as he was the founding editor of a new journal called *Nature Genetics*.

I will always be grateful to Kevin and that journal for accepting my first paper from the Vogelstein lab on defining the DNA-binding consensus sequence for the tumor suppressor protein p53. *Nature Genetics* published it on page 45 of that first issue, after *Nature* rejected it, and it has stood the test of time.

The book begins by describing Kevin's arrival to Hong Kong on Monday November 18, 2018, to attend a conference on CRISPR when news broke on Twitter that babies genetically altered by CRISPR might have already been born—#CRISPRbabies was trending, and news of YouTube videos made by 34 year old Chinese Scientist He Jiankiu described what he had done and that "two beautiful little Chinese girls, named Lulu and Nana, came crying into this world a few weeks ago."

Kevin had a front row seat to He Jiankiu's presentation and questioning at the conference that was seen by many around the world. Unlike what someone said on social media that Jiankiu was being inappropriately celebrated, Kevin "felt we were watching a dead man walking."

Kevin recounts discoveries by Emmanuelle Charpentier, Jennifer Doudna, Feng Zhang at Broad and George Church, at Harvard. He touts the vast reaches of CRISPR and its impact on disease and life in general, and the "CRISPR Craze" as referred to by Science and the lay press.

Kevin recounts his experiences as *Nature Genetics* editor, the BRCA1 discovery, the sequencing of the human gene and how the cost went from $2 billion to $1,000. He goes into ethical concerns with CRISPR, as well as the impact of basic science to lead to such an important discovery that is already showing impact on human disease.

CRISPR is a breakthrough of immense magnitude for gene editing. It allows "surgery" on the genetic code or for those who use it to "play God." Davies describes comments by Nobel Laureate Bill Kaelin from a piece in the *Washington Post* championing basic research on cancer rather than "razzle-dazzle moonshots:" "The CRISPR gene-editing technology that will revolutionize medicine and agriculture emerged from studies of bacteria and their resistance to viruses."

Eric Lander, who now works for the Biden Administration, touts CRISPR as "the most surprising discovery, and maybe the most consequential discovery, in this century so far." Much is riding on this, as Fang Zhang, who is a faculty member at the Broad Institute, has founded five companies in five years.

James Watson credited Charpentier and Doudna with the biggest discovery since the double helix and further said, "If it's only used to solve the problems and desires of the top 10%, that will be horrible," and further stated, "we have evolved more and more in the past few decades into an inequitable society, and this would make it much worse."

Kevin Davies takes us on a treat to the Kavli Prize celebration, including some small talk, the event, Alan Alda, the sumptuous menu and the laureates mingling with King Harald of Norway. He notes something most probably haven't thought about, that Doudna literally has the word "DNA" in her name. He takes us to the debate in the U.S. Senate in 2017, where Senator Susan Collins of Maine expressed concerns that science has outpaced policy.

With a flurry of activities and multiple companies and patent disputes, the debate also reached the Vatican, where Pope Francis recognized scientific progress but also said that not everything that could be done is "ethically acceptable."

> Steven Hawkings before his death predicted that gene editing would lead to "superhumans" and went on to say "once such superhumans appear, there are going to be significant political problems with the unimproved humans, who won't be able to compete."

And here's a scary quote from Australian geneticist Daniel MacArthur, who tweeted, "my grand-children will be embryo-screened, germline-edited. Won't 'change what it means to be human.' It'll be like vaccination."

But in 2018, He Jiankui's career crumbled overnight without fanfare.

While NIH Director Francis Collins has been conservative, and leading scientists called for a moratorium, George Church has said "I just don't think that blue eyes and [an extra] 15 IQ points is really a public health threat…I don't think it's a threat to our morality."

More shockingly, Steven Hawkings before his death predicted that gene editing would lead to "superhumans" and went on to say "once such superhumans appear, there are going to be significant political problems with the unimproved humans, who won't be able to compete. Presumably they will die out or become unimportant. Instead, there will be a race of self-designing beings who are improving themselves at an ever-increasing rate." Scary stuff, I must say.

Davies goes into the history of the human genome project and gives details of how CRISPR works and its broad classes and different nucleases. In her keynote at a Banff conference in January, 2020, Doudna proclaimed "precision editing of any genome is within reach."

I loved reading the story of Francisco Mojica, a microbiologist interested in halophilic (salt-loving) bacteria, and noticed in 1992 repetitive sequences that make up 2% of prokaryotic DNA. By 2001 he came up with the CRISPR acronym that stands for *clustered regularly interspersed short palindromic repeats*. By October, 2003 he submitted a paper to *Nature* entitled "Prokaryotic repeats are involved in an immunity system." The paper was declined by *Nature* and by PNAS, and a year later submitted to an evolution journal.

Six months later he heard from the editor and three months later the paper was accepted. Mojica told Kevin Davies, "I remember those two years like a nightmare," and said "when you have something so big in your hands and you send it to the very good journals—and all of them agreed it was not interesting enough to be published—you think is it me who is crazy or something else?"

Another researcher, Gilles Vergnaud in Paris, had similar frustrations when doing research for the French Ministry of Defense, motivated by fears of Saddam Hussain's use of bioweapons, submitted in 2003 a paper with CRISPR in the title and notions of defense mechanisms.

This was passed on by PNAS and other journals until it was published in 2005.

Most everyone in academia will sympathize with these experiences and acknowledge that the peer review system (and the grant review systems) have gotten much worse over the last 20 years.

Kevin Davies describes how he originally met Jennifer Doudna at a HHMI meeting in Chevy Chase, MD, back in 1998, when she was a young rising star and new HHMI Investigator.

When she was 12 years old, Doudna's father, an English Professor at University of Hawaii, left her a copy of *The Double Helix* which eventually captured her imagination. During high school, her guidance counselor told her "girls don't do science," which only intensified her interest in science.

She earned her PhD with Jack Szostack at Harvard in 1985. Szostack, who was an RNA biochemist, won the Nobel prize—and it was during her research with him that she became very interested in RNA and its potential enzymatic activity.

Doudna also worked with another Nobel Laureate and RNA biologist, Tom Cech (also former HHMI President), in whose lab she met her future husband. She eventually started a lab at Yale and then moved to Berkeley. More details are given about her brief stint as a VP at Genentech, and that she was allowed a return to Berkeley to reclaim her HHMI investigator role and work on CRISPR. Davies goes into Charpentier's career and fame in Europe, more about Fang Zhang, and others.

Doudna and Charpentier met in March, 2011 for the first time in Puerto Rico. Charpentier, the more junior of the two, told Doudna about her upcoming results in Nature and offered to collaborate. Martin Jinek in Doudna's lab worked on the collaboration and recounts the brainstorming that led to the idea of a single guide RNA that could be used to reprogram any sequence. In 2012, the collaborators submitted a paper to Science noting potential for gene targeting and genome editing that was accepted in 12 days.

Doudna and Charpentier went on to win the 2020 Nobel Prize in Chemistry for their CRISPR discoveries.

A bit of history I did not know: the founding editor of Cell (in 1974), Ben Lewin was a Nature Editor. He would sell the journal to Elsevier in 1999 for more than $100 million.

> “As for the somewhat scary comments by Church and Hawkings, I hope our scientific and political leaders keep us safe from a strange dystopian future that might be inflicted by the CRISPR revolution.”

I was grateful in 1993 that Dr. Lewin accepted my paper on *WAF1* in *Cell*, and before Steve Elledge (now at Harvard) called Bert Vogelstein to tell him about a gene they cloned from a yeast two-hybrid system encoding a protein they called p21(Cip1) that inhibits CDK2. There was a brief time when Ben Lewin was the only one in the world who had the two papers with the same gene sequence for *WAF1* and p21(Cip1) that would be published back-to-back in *Cell* in late 1993.

Davies's book is an interesting history of many individual scientists and their contributions and collaborations to the CRISPR story. This story is also about the 7,000 or so genetic disorders described by the late Victor McKusick who edited "*Mendelian Inheritance in Man*," and was the founder and leader of the Human Genome Organization (HUGO).

I was fortunate to meet Dr. McKusick during my training at Johns Hopkins including a visit with him to the top of the Dome at the Johns Hopkins Hospital in 1994. It was an extremely rare honor for me at the time (arranged by my post-doc mentor Bert Vogelstein) as it has typically been reserved for the chief residents in medicine at Hopkins (it was also enjoyed by others in the lab who I invited to join us).

Dr. McKusick was no longer chair of medicine at the time but would be seen occasionally at Medicine Grand Rounds on Saturdays when other giants of medicine, such as Dr. Harry Klinefelter (Klinefelter Syndrome), would be sitting there in the audience.

I later heard Dr. McKusick give a wonderful lecture at Hopkins that was recorded during an Interurban Clinical Club meeting. Davies writes "if he were still alive, the father of medical genetics would be in awe at the progress we've made in documenting the myriad ways in which our genetic software can be corrupted, not to mention the potential of delivering a patch to fix those errors."

Hopefully this clinical translation with CRISPR can be done safely for the treatment of genetic diseases as we are already seeing, and there would be more impact in cancer for example using CRISPR-engineered CAR-T cells.

As far as embryo editing, I sincerely hope that this is completely outlawed and that we undertake a moratorium of several decades while we gain much more knowledge about collateral damage to the human genome. As for the somewhat scary comments by Church and Hawkings, I hope our scientific and political leaders keep us safe from a strange dystopian future that might be inflicted by the CRISPR revolution.

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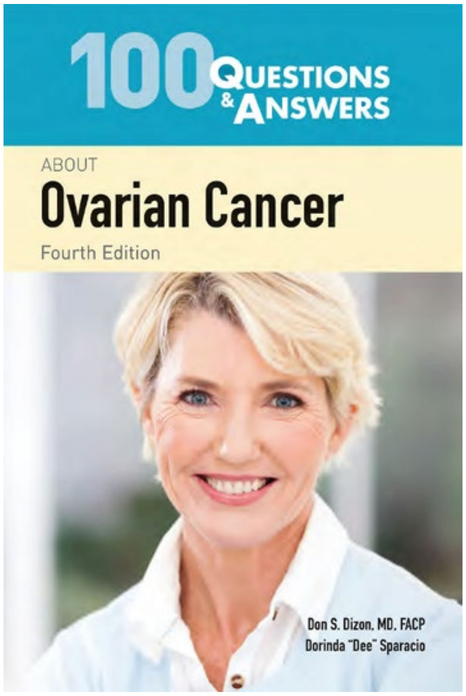
100 questions and answers about ovarian cancer



I have been at Brown University coming up on three years. We are building and growing our cancer center at Brown in pursuit of NCI designation during the coming years.

I came here because of amazing colleagues doing great work in science, clinical care, clinical trials and community outreach. One of those amazing colleagues is Dr. Don Dizon, professor of medicine at Brown who leads the pelvic malignancies program at Lifespan Health System and has been spearheading our community outreach and engagement efforts at our cancer center at Brown.

Don needs no introduction as a fellow of ASCO, leader in oncology education, LGBTQ advocate, and social media rockstar who also embraces new platforms such as TikTok—where he has made many public service announcements. He is also a national leader in bringing the potential for social media in oncology to fruition.

I recently discovered the fourth Edition of his popular book about ovarian cancer, and felt that I should read it to learn something, and that I should take this opportunity to tell others about it.

The book is an incredible resource that has evolved over 15 years to the current fourth edition and is intended to help patients "with ovarian cancer, their families, significant others and loved ones."

Dr. Dizon writes "The fact is: We can cure ovarian cancer, but even when we cannot, we can help you live with it, too." Much progress has been made and Dr. Broach mentions that the book provides information to answer "questions patients have while navigating their unique and often complex treatment plans."

The first part of the book provides basic information about ovaries, their function, what it means to have cancer, cysts, including their different varieties. There are diagrams with details of the anatomy and descriptions of the physiology.

A basic description of cancer and metastases in lay terms is provided along with dispelling some myths and misconceptions about what cancer is not. For example, cancer is not an infectious disease, and also if your mother had ovarian cancer, it doesn't mean you will definitely develop the disease (although you may be at increased risk). The book provides information to dispel the myth that ovarian cancer is a death sentence. The patterns of spread of ovarian cancer are discussed. The Krukenberg tumor is explained.

The risk factors, diagnosis, and staging of ovarian cancer are covered in part II of the book. While the book focuses on epithelial ovarian cancer, non-epithelial ovarian tumors are mentioned. Recent knowledge about potential origins of ovarian cancer in fallopian tubes is discussed as are implications for whether removal of the ovaries might be needed to prevent the disease.

The epidemiology and incidence of ovarian cancer are described as are the subtypes of epithelial ovarian cancer. Germ cell tumors, choriocarcinomas, sex cord-stromal tumors and teratomas are explained. Because the granulosa-cell tumors make hormones, patients become symptomatic at an earlier stage which generally portends a more favorable prognosis for these tumors due to their earlier detection.

Gene mutations that can lead to ovarian cancer are explained including those that are inherited or acquired. The BRCA1 and BRCA2 genes are explained, including the risk of ovarian cancer they confer when mutated. Other genes that increase susceptibility to ovarian cancer are mentioned.

Hormonal therapy and talc are covered. The many varied symptoms of ovarian cancer are discussed. Dee commented about her own diagnosis and experience in 2005 when she developed some non-specific symptoms. She makes the point that awareness of the symptoms is important.

The authors explain Ascites, along with its treatment, and when it occurs as part of advanced ovarian cancer. The diagnosis of ovarian cancer is discussed, along with blood tests such as CA-125. Dee provided some of her experiences and anxieties with the CA-125 test. Dee also reflects on PET scans.

The authors present the latest FIGO staging system of ovarian cancer, as well as the differences between stage and grade. Information about prognosis is provided. Dee comments about the benefits of second opinions.

The treatment of ovarian cancer is discussed in part III of the book. Dee described her strategy for care at a cancer center near her and the importance of access to a multidisciplinary team of specialists and ancillary services. The authors also address surgical options, including fertility sparing surgery. Dee comments about the availability of both IV and intraperitoneal chemotherapy treatments and how they are administered.

Various treatments besides chemotherapy are discussed along with side effects, including angiogenesis inhibitors, and different available PARP inhibitors. The authors explain HIPEC, treatment monitoring, radiation and immunotherapy—including vaccines.

Participation in clinical trials is explained. Dee explained her participation in a clinical trial and the reasons behind a later decision to not participate in a second trial for recurrent ovarian cancer. There is a discussion about ovarian cancer during pregnancy along with options for managing it. Complementary and alternative medicines are covered. Dee provided her valuable insights about these therapies.

Part IV deals with treatment-related side effects, diet while on treatment, treatment at older age, vitamins, growth factors, managing nausea, neuropathy, among other issues. The authors addresscConcerns about sex and intimacy in the context of cancer treatment, hot flashes, depression, and "chemo brain." Part V is more focused on symptom management and palliative care and part VI is focused on relapse and options for treatment, and part VII addresses "if treatment fails," hospice, DNR, TPN, health care proxy. Part VIII provides information about prevention, screening, and advocacy.

This is clearly an invaluable and rich resource with immense amounts of information to help patients and their loved ones. It is highly recommended for the entire continuum of the disease course. Other resources and organizations are mentioned as well as information about support for patients with ovarian cancer. This book about ovarian cancer is a model resource for patients and the lay public that should be emulated for other tumor types.

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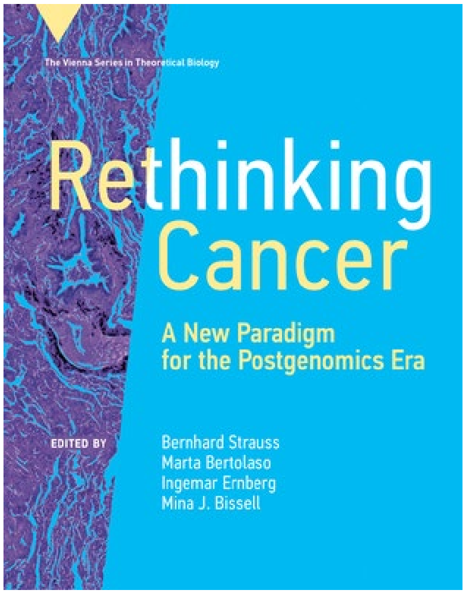
Rethinking Cancer: A New Paradigm for the Post-Genomic Era



I have met Dr. Mina Bissell a few times in my career, and have invited her to speak in the past at an international conference I organized on the topic of drug resistance in cancer.

She is a leader in the field of cancer research, the tumor microenvironment, and an inspiring woman scientist and mentor by all accounts. I was therefore very curious, as most people in the field should be, to see a book edited by her and her colleagues about the topic of rethinking cancer in the post-genomic era. We all need new ideas and different perspectives in oncology.

I appreciated in the preface the mention of reduced spending on cancer research, in this case in the UK, and the impact of the COVID pandemic on delays in cancer care. The genomics revolution and precision medicine need to fulfill their promise and so we need more fresh insights into how to prolong life for patients with advanced cancer.

We have powerful molecular tools, computational methods, and more knowledge about cancer than ever before. But as most everyone knows, cancer is complex with heterogeneity between patients with the same disease or even within the different cells of the same patient. "This ubiquitous observation has led to the declaration of a 'complexity crisis' in the cancer genomics field."

Beyond genomics the many other 'omics' are now of much focus, hence "post-genomic" but now with a recognition that precision medicine in oncology is much more difficult than previously anticipated, and the system needs a "reboot," "we've tried genomics, with only modest success in curing cancer, and now we need to move on to something else—but where to? That is what this book is about."

This, the editors point out, was "a failure clearly not due to lack of financial investments," but rather "an incomplete or incorrect theoretical framework in our attempts to explain carcinogenesis." The editors "are united by the view that it is paramount to revise the current somatic mutation paradigm if we are to make progress in finding a cure for cancer." They acknowledge that less well represented in the book are the areas of inflammation and cancer immunology.

On the systems dimension of cancer, Dr. Strauss says: "What we have learned from complex systems, however, not only in biology, is the fact that their inherent nonlinearity often produces outcomes that seem counterintuitive to human 'rational' thinking. Thus, when human intervention interferes with such systems, the results can appear often 'paradoxical,' as for example when perturbing cancer with different treatment modalities."

This comments hits home because my own research is focused on killing cancer cells (every last one including by boosting the immune system): "Taking a complex dynamical systems logic into account from the start, seemingly paradoxical actions, such as not attempting to kill all cancer cells or choosing lower than the maximum kill dose of a given drug, make perfect sense and can deliver desired results in cancer treatments."

The concept of "cellular attractor" is introduced, as are ideas around cellular phenotypic traits, such as variable protein concentrations within a population of otherwise similar cells, plasticity, adaptive responses, and that there are millions of simultaneously occurring chemical reactions in an "ultra-high molecular density environment" within cells.

"What a systems perspective of cancer teaches us is that we need to go off-piste a lot more than we normally do and explore many more areas outside the well-funded highways to professorship," Dr. Strauss writes. He then points to the 99% of "junk" non-coding DNA, the so-called dark matter of our genome, as "highly relevant to our understanding of cancer genomics."

Evolutionary theory and single cell analysis have empowered the field to analyze heterogeneity and the temporal dimension of cancer. I would say that Darwinian theory does impact cancer research now especially with studies for example in our own work that focus on hypoxia, drug resistance, and other selection pressures in tumor evolution.

> [Mina Bissell] is a leader in the field of cancer research, the tumor microenvironment, and an inspiring woman scientist and mentor by all accounts. I was therefore very curious, as most people in the field should be, to see a book edited by her and her colleagues about the topic of rethinking cancer in the post-genomic era.

This too is near and dear to us and it is certainly appreciated the mention that there should be more of that in the field. I also appreciate the idea of evolutionary dynamics and unanticipated ways for how we may need to treat some cancers without aiming for maximal cell killing. I would say a good example is colorectal cancer and treatment with anti-EGFR agents.

We do aim for maximal cell kill, in fact, I normally tell my patients that my approach in designing a treatment strategy is to "take our best shot at this." I think this book would argue that taking our best shot may not mean killing every tumor cell when we might have the chance.

In the case of anti-EGFR therapy, I am fascinated by the findings of Scott Kopetz (MDACC) and others that resistance mechanisms extinguish when patients are taken off therapy so that therapeutic re-challenge at a later time has efficacy. I do not believe this insight came from basic science but rather from the evolution of applied technologies such as liquid biopsies that could monitor the levels of KRAS resistance mutations for example (or others) and see over time that their levels extinguish suggesting the possibility of re-challenge therapy.

The idea that different tumor cells, depending on their evolutionary history of their own genomes will have different adaptive responses to selection pressures or microenvironment forces deserves more research focus (and of course is interesting).

The idea that a goal should be "to induce cancer cells to switch their rewired cancer genome "back to normal" is great. But I would disagree that "clearly, such a systemic switch cannot be achieved by targeting single mutations in single genes."

I would argue that it can be achieved with targeting master regulators such as p53 that is the most commonly mutated gene in human cancer, and in fact we have worked for the last two decades to restore that pathway or its transcriptome to achieve a cancer therapeutic response.

We have uncovered different ways this can be achieved from involvement of p73 to activation of a cancer-specific integrated tress response that bypasses p53 mutations and kills tumor cells. I would also argue that much has been achieved using those imperfect cancer cell lines that are no longer in vogue, including impact on patients who couldn't wait for the better models.

This in no way should keep us from developing better models, but also, we shouldn't abandon ways that have led to success. I like to think that we will cure more cancers, but the reality is some advanced cancers may not be curable no matter what we do.

And this comes from one who will turn every stone to find a treatment to help a given patient. I should add that I've seen one of my own patients get out of hospice a few years ago and live many months with 'miraculous' targeted therapy and think there needs to be some sort of reset in our field knowing things like that can happen—the progress is impacting people's lives despite how advanced cancer gets.

The book is divided into sections that focus on different dimensions from redefining the problem through the theory dimension to the systems dimension, the time dimension, and the microenvironment dimension of cancer. There is an underlying tone in the book that the incredible impact of research on the tumor microenvironment and insights into the complexity of cancer has been underappreciated.

While this may be perceived as such by some, I personally believe otherwise, that the contributions made by the TME field have been incredibly valuable and do shape the mainstream.

I think it is common for clinicians in 2021 to fully understand the complexity of cancer and its microenvironment and to now blame that TME as well as tumor evolution, heterogeneity and the immune system, on why treatment fails.

I like the idea that tumor heterogeneity has emerged as a "master hallmark" that we need to understand much better to develop better treatments. I would also like to say that reading this book, one gains a new appreciation that it is an understatement to say that cancer is "complex." I think we need to build and we need breakthroughs. I would be careful with "reboot" because as a clinician I also believe in "do no harm" and that we shouldn't necessarily abandon what we are doing until there is clear evidence that doing things differently will actually work better.

> "There is much to learn from this book, from different perspectives that we need to take seriously to actual insights about cancer gained from network science, plastic and rigid networks and how they are altered in cancer and how cancer stem cells are impacted."

The physical sciences have much to offer as does information science. They are helpful in providing different vantage points to try and make sense of complex biological systems. Dr. Huang refers to a "rigid mentality" and the "ceaseless quest for ever more powerful ways to kill cancer cells."

I am one of those, and would not mind doing something different (including collaborate with those who have a very different perspective) if I really believed it was better. I agree we need to be open-minded and I think our strategies have evolved in recent years to be much more purposefully tumor microenvironment-directed.

I still think cancer stem cells are important and we shouldn't forget them within all the complexity. I totally agree that ALL treatments have limitations in the cancer clinic, not to mention toxicities. But overall, there is forward motion. Yes, we need to do much better "to bend the curves" as clinicians often say about improving those Kaplan-Meier curves. I disagree that wrong strategies are perpetuated because we inadequately explain treatment failure. I think the whole field of oncology and translational cancer research is focused on understanding treatment failure and doing better, whatever it takes.

This means working with colleagues with differing expertise and understanding more about cancer's complexity—much is being learned now. There is much food for thought in this book about what we know and don't know. Dr. Huang presents a case for formalizing a complex system as a network of interactions of its components. And that this is aided by new technology such as single cell RNA-seq.

Dr. Huang describes systems dynamics, combinatorial interactions among components, the impact of constraints on interactions on characterizing a system, nonlinearity, the landscape of genetics and epigenetics, and the fact that most cancer treatments don't work as desired. The point is made that treatment "also contributes to recurrence in an active manner."

Hyperprogression after cancer treatment (including by immune checkpoint blockade) is discussed and the impact of preclinical models on understanding effects that may be hidden in Kaplan-Meier curves.

Dr. Huang also gets into an interesting topic of "Process Spontaneity: The Fundamental Inevitability in Multistable Systems," and the concept of "attractor states." A detailed theoretical framework is presented and then some molecular mechanisms are discussed.

The author proposes "new research programs" such as ones to "elucidate the molecular pathways of stress-induced stemness," "design and analyze experiments in a refined, quantitative, and theory-guided manner to uncover dose regimes of intervention that minimize the 'backfiring'," "examine the exceptional responders both in the positive (cure) as well as negative sense (treatment-induced progression) as real biological phenomena and not as statistical flukes," and "we must be open to new schemes for trials that currently limit the early studies of novel classes of treatment to patients who have failed all therapies—precisely because previous treatment may have altered and diversified cancer cells on the epigenetic landscape, rendering them essentially untreatable."

There are good ideas here, although it remains to be seen whether actively trying to minimize 'backfiring' will impact on patients.

There is much to learn from this book, from different perspectives that we need to take seriously to actual insights about cancer gained from network science, plastic and rigid networks and how they are altered in cancer and how cancer stem cells are impacted.

There is an interesting concept, that "different drug design strategies are required against early and late-stage tumors." Early tumors have central nodes for targeting while late tumors have "more rigid cellular networks."

More exploration of predictions from network science are proposed. Dark matter, computational science, and Artificial Intelligence (AI) are further discussed. Drs. Scott, Basanta and Marusyk make a major point that Darwinian evolution rather than "mutationalism" is what is needed for new cancer therapies.

"In contrast to the helplessness in dealing with the bad luck of mutation-driven process, embracing a Darwinian explanation enables a much more proactive attitude, as both diversification and selection could be subjects of clinical interventions." Specific strategies are suggested for such interventions. "Rather than maximizing the short-term tumor cell kill rate, it might be possible to optimize chemotherapeutic treatments to increase the rates of genomic alterations, thus driving down fitness of populations of tumor cells."

Epigenetic drugs "can be potentially repurposed with an explicit consideration of the impact on phenotypic diversity and plasticity." Consideration is given to "adaptive therapy scheduling based on evolutionary tradeoffs," "to forestall the expansion of resistant sub-populations." "Atavism" and "reversion to an ancestral phenotype" is covered in a chapter by Drs. Bussey and Davies. Specific directions are proposed for translation of the ideas that are discussed.

Dr. Larry Norton writes a chapter about "Time and Timing in Oncology." Dr. Norton gets us to consider that while so much progress has been made, including with targeted therapies that attack the Achilles heel of some cancers and can work, when they don't we don't question the "original paradigm" or metaphor.

"Achilles does not stand still." This is the concept of time and change within a tumor. We need to learn better "how to shoot them [our arrows] at a target in motion." "It is for this reason that the science of drug scheduling needs to progress in parallel with the science of molecularly targeted drug design."

He gets into the "log-kill hypothesis," "Gompertzian-like sigmoid growth," and makes the point that a high response rate does not equal cure. It is also nice to read an explanation of the Norton-Simon hypothesis "it is all about rates." "Explicitly, a given drug at a given dose kills a higher fraction of cancer cells in faster- growing, small tumors than in larger, more slowly growing masses of similar biology." Mathematical models, time, and timing are important, according to Dr. Norton.

Dr. Valerie Weaver and colleagues delve into desmoplasia, stiffness, mechanotransduction, metabolism, nutrient sensing, chromatin interactions as important areas for study in cancer. Metabolism, glycolysis, low pH of cancer is covered by Drs. Zdralevic and Pouyssegur. The Warburg effect is explained in detail as are some therapeutic opportunities. Immune evasion and ferroptosis are also discussed. A chapter on vascular corruption in cancer covers endothelial heterogeneity, tumor-endothelial cell interactions, various chemokine and growth factor pathways, and other chapters cover metastasis and the "niche."

The editors end with a glimpse of the future. This includes education and translation to get to "transformative innovation."

CANCER HISTORY PROJECT

The history—and future—of oncology, according to directors of the first three NCI-designated Comprehensive Cancer Centers

"There couldn't be a better time to be in oncology"

By Katie Goldberg and Alexandria Carolan

Directors of the first three NCI-designated Comprehensive Cancer Centers are learning from the past, starting with the National Cancer Act, and mapping an equitable future for oncology.

The Cancer History Project July 29 convened panelists Candace S. Johnson, president and CEO of Roswell Park Comprehensive Cancer Center, Craig B. Thompson, president and CEO of Memorial Sloan Kettering Cancer Center, and Peter WT Pisters, president of MD Anderson Cancer Center, during a two-hour Zoom session moderated by CHP co-editor Otis W. Brawley.

"50 years later, after we look at what many refer to as Nixon's War on Cancer, it's time for an after-action report, where we sit back and assess where we've come from, what we've done, and that's how we figure out where we're going in the future," Brawley, Bloomberg Distinguished Professor of Oncology and Epidemiology at Johns Hopkins University, said during the free virtual panel.

After the National Cancer Act of 1971 was enacted, these three distinctive institutions "got designation without even applying," said Johnson.

"I really believe one thing that should be emphasized today is that, by starting out with three exemplars, and then by putting into place a set of criteria, [the comprehensive designation] became an aspirational goal," Pisters said.

"Our center grant came because we had 54 funded NCI grants. And the NCI said, 'You're driving us crazy, because you all want the same resources,' and made us bundle them all," Thompson said. "We complained it was so much paperwork. We think about the paperwork today—they were complaining in 1964 there was too much paperwork. And the NCI, at least according to our records, threw up their hands and said, 'Fine, put them all in one center grant.'"

A full transcript and video of the panel are available here, through the Cancer History Project.

"We don't want to lose our past"

The way the three institutions were founded—and funded—couldn't be more different.

"In 1898, you were more likely to die of an infectious disease than cancer, perhaps, but [Roswell Park founder and namesake] really saw a real need for this," Johnson said. "And he also thought, and this was very revolutionary for the time, that the government should support this research."

Memorial Sloan Kettering was founded in 1884 as a private hospital, with philanthropy, Thompson said. "It was actually built with round rotundas because they weren't really sure that it wasn't a virus or a bacteria, so they built a hospital with round rooms so there were no corners for microbes to lurk in."

MD Anderson, however, was founded in 1941 by the the Texas legislature:

"The legislature at that time voted to create a state cancer hospital that would be devoted to research to cancer treatment, and positioned that cancer hospital under the jurisdiction of the University of Texas and its board of regents," Pisters said. "And the hospital, as you alluded to Otis, received tremendous support from Monroe Dunaway [Anderson], who was a cotton merchant."

Talking about the value of history, Johnson held up a carved wooden box.

"This is a tobacco box that was Roswell Park's," she said. "It sits on my desk. And I don't use it for tobacco anymore.

"We don't want to lose our past," she added.

All three centers take preserving their history seriously. Roswell Park has a historian on staff, and MD Anderson and MSK both maintain extensive archives.

Pisters expressed concern about preserving our present, too.

"A lot of old history can really be put together with memos and letters that are in paper files. And now we've moved to a digital environment—I'm completely paperless myself. And every now and then I'm wondering, how is the history of this period ever going to be documented? Because it's in a bunch of deleted emails, it's on a bunch of servers," Pisters said.

"How are we going to take the archivists of the modern era and help them to chronicle today's history?"

A "devilish" question

"For us, team-based science started in 1960," Thompson said. "They [Alfred Sloan and Charles Kettering] both believed the research institute, a hospital, had to be separated. And it took us until 1960, 15 years of separate governance, but overlapping governance, to realize they were best together."

Today, do matrix centers benefit even more with regard to team-based science?

"This is sort of devilish of me," Brawley said. "What's the advantage of a matrix center versus a center that's freestanding?"

"The clear benefit of the matrix environment," Pisters said, "is that you've got a rich ecosystem, and you can be a beneficiary of the talent and the resources, the infrastructure, at the university, and that can foster tremendous collaboration and lots of opportunities."

Said Thompson, "Academic medical centers that are with a matrix cancer center have one tremendous advantage that we don't have, and that is a primary care network," Thompson said.

However, "I think all of us on this panel would say the advantage of a freestanding center is you have more control," Johnson said.

Pisters agreed. At a freestanding center, "we can shed ourselves of many of the funds flow issues, the internal politics associated with that, and we can focus on making cancer history," Pisters said.

"And that, really, is a lot of the special sauce that exists in independent cancer center environments, where you're freed from a lot of the politics, funds flow, and you can focus on what's important."

The panel discussion demonstrated that oncologists are asking some of the same questions they did in 1971.

"The biggest debate in Congress [in 1971], if you read those records, was whether the new money should be a contract or a grant," Thompson said.

"And thank goodness, the scientific community stood up and said, 'It cannot be a contract. This is not just delivering this number of doses. We need to investigate the science of this and to have those investigator-initiated ideas, and a way to do that.' It's a time where that debate's happening again."

Funding, however, remains a key concern.

"I'm not sure we're always as effective lobbyists for getting more money from the federal government for the NCI," Johnson said. "I think we need to be more bold, and maybe the general public, especially coming out of COVID, where research is so important, can help us with that."

Said Pisters, "Now, we're in an era where we can get a COVID vaccine generated and into people's arms in six months. These are unbelievable triumphs of science that the general public is becoming much more aware of, and therefore, hopefully, continuing the long-standing, bipartisan support for NIH funding."

Serving catchment areas, and beyond

Community outreach and engagement is a "uniquely American" concept, Pisters said.

Countries with single-payer healthcare systems and "have better health outcomes than the United States use a jurisdictional approach to cancer prevention and screening," he said. Whereas the U.S. created COE "as a best practice, or as an adaptation, to try to extend prevention and screening benefits, as well as anti-cancer living benefits, to larger populations, not just those who enter our organizations.

"So, it would be important for us at a policy level to learn lessons from other countries that are, frankly, better at this than we are," he said.

The U.S. also has a unique challenge with underserved populations that do not trust their health care systems to come up with solutions that are in their best interests.

"I applaud the NCI for focusing on this because it, and quite honestly, many of our efforts that we've done in cancer, really helped us to reach folks for COVID vaccines because they trusted us, because we've spent a lot of time in trying to develop trust in many of these groups that don't trust us," Johnson said. "It's helped us in so many ways, education, screening, and so forth."

Outreach efforts can be bolstered by strong partnerships, both locally and as part of the global community.

"The critical things that we've seen, that we uniquely can do, are some of our aspects of immigrant health and cancer disparities," Thompson said. "We've used the UN, a unique resource we have, to do reverse translation."

Speaking of global outreach, Pisters said, "we reached the conclusion that single institutional efforts are highly inefficient. And our resources are probably best allocated in partnership with the WHO, with UICC, where we can come together and take full advantage of their talent, their infrastructure, their footprint, in some of these areas of the world where there's massive unmet need."

A diverse workforce is essential for community outreach and engagement, Johnson said.

"One of our faculty members is a member of the Seneca tribe, so we have a big study and looking at obesity and trying to make connections in the indigenous population, and I want to tell you, it's a whole other level of mistrust, if you will. And so we've made great strides in helping to, in our screening programs, to get these folks in," she said.

"I don't think it's enough just to go into our community and do the kinds of community engagement kind of things that we're doing, as it relates to [Cancer Center Support Grants]," Johnson said. "I think that the way we're going to really make connections is we have to have more physicians, nurses that are African American, or indigenous population, or LGBT. We need to be more."

Thompson agreed. "We needed to understand that we don't have enough diversity in our senior ranks, particularly of our physicians and our senior researchers. We are not as diverse as the community we serve and we need to do better."

MD Anderson is taking steps to build diversity, equity, and inclusion into the cancer center's core strategy, Pisters said.

"Diversity and inclusion are not the same. Diversity is a descriptive fact, inclusion requires acts—and deliberate acts, and strategy," Pisters said. "And that's the conversation that we've had as we embark on a big institutional effort on DEI."

"The last frontier"

Where is the science of cancer headed? The directors theorized:

"The problem is cancer metastasizes, and that's the last frontier," Thompson said. "There aren't tumor suppressors of metastasis. And so we've got a whole new frontier, because that's, unfortunately, why there's still residual cancer that we can't handle. And, ultimately, when we understand the biology of that, we'll get to the future."

For Johnson, the answer is immunopharmacology.

"I think that what all of us are doing in the immune space, in the immunotherapy space, is really exciting," she said. "I mean, we're seeing the 'C-word'—cure—in patients that you just wouldn't have seen this before."

The past decade in cancer progress has been like no other, Pisters said.

"When you look at the strength of our institutions, you look at 51 Comprehensive Cancer Centers across the United States, there couldn't be a better time to be in oncology," he said. The kind of innovations, the discovery, the amazing things that are going to happen in the next 10 years... I can't wait to see it happen."

Oncology has come a long a way, Brawley said.

"I'm just going to end by saying, you know, I saw a guy yesterday. He's had stage four non-small cell lung cancer for 12 years. I don't think I would have thought that possible 20 years ago."

> "Other developed countries that have single payer systems ... that have better health outcomes than the United States use a jurisdictional approach to cancer prevention and screening. It would be important for us at a policy level, to learn lessons from other countries that are frankly, better at this than we are."
>
> *– Peter Pisters*

IN THE ARCHIVES

CANCER HISTORY PROJECT

Midway through the 50th anniversary year of the National Cancer Act, what have we learned?

When the Cancer History Project launched in January, co-editors Otis Brawley and Paul Goldberg laid out a plan to build a lasting resource for the history of oncology (*The Cancer Letter*, Jan. 8, 2021). It was "the beginning of a process of storytelling."

Since then, we have published 11,805 articles—of which 11,428 are *The Cancer Letter* archives. Of the other 377 articles, published by our 43 contributors, 150 are primary sources, 138 are profiles of people, and 21 are profiles of institutions.

The Cancer History Project has been growing at a rate of over 50 articles a month, and our readers keep exploring—the average visitor reads eight articles per visit. We've reached approximately 31,000 unique visitors, who have read our articles 500,000 times.

To help *The Cancer Letter* readers follow along, we launched the In The Archives column, which profiles the latest articles for the week and highlights topics from the Cancer History Project editorial calendar.

Our work has gone beyond building a platform for contributors to help preserve their histories. We have taken an active role in recording oral histories, digging up unpublished books, digitizing archives, and uncovering stories that could otherwise have been lost.

You can read about Joseph H. Ogura, an otolaryngologist who fled California during World War II to avoid internment. Ogura, along with his iconic (but empty) pipe, helped develop partial laryngeal surgery in which one of the two vocal cords is left intact.

Or Eva Bateman Noles, an oncology nurse and historian who was the first Black graduate of her nursing school, graduating first in her class—but was unable to attend her own graduation party at a whites-only hotel. She went on to become chief of nursing services and training at Roswell Park.

Or, in case you needed a reminder that even Donald Pinkel, "who introduced the word 'cure' to cancer," got rejection letters, read a letter from the *Journal of Pediatrics* rejecting his 1971 article, "Drug Dosage and Remission Duration in Childhood Lymphocytic Leukemia," later published in *Cancer*—side by side with a glowing personal letter on MD Anderson letterhead from Emil Frei about the same article.

Looking at our most-read articles, it's apparent that our readers and contributors share our interest in storytelling. There is a clear focus on the people and the stories that shape our history—and inform science. Here are the top 5:

- **Video:** Amy Reed, physician and patient who "moved mountains" to end widespread use of power morcellation
- **Book:** Simone's Maxims: Understanding Today's Academic Medical Centers
- **Oral history:** To NCI designation through difficulty: How KU's Roy Jensen made it happen
- Remembering Jane Cooke Wright, a Black woman, who was among seven founders of ASCO

- Gordon Zubrod's panoramic vision shaped modern clinical cancer research

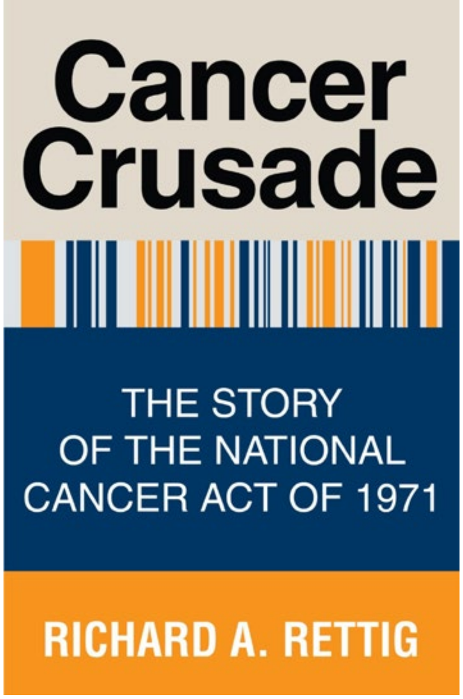
Our goal continues to be to create a starting point for a broader discussion of history and community, and, with that in mind, on July 29th we ran our first virtual panel, featuring cancer center directors from the first three NCI-designated Comprehensive Cancer Centers. A summary and recording of the panel is available on page 38.

This is not a one year project, and it's never too late to join us. To become a contributor, please contact admin@cancerhistoryproject.com. Our 2022 editorial calendar will be available soon.

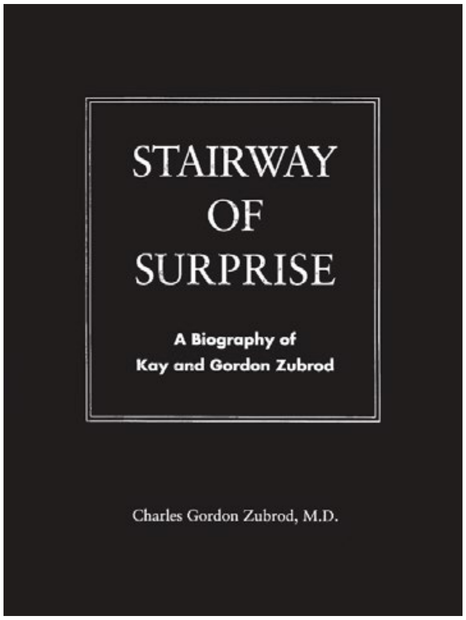
Highlights

In honor of *The Cancer Letter*'s Summer Reading Issue, here is a selection of books and articles you might have missed, or might want to revisit at a leisurely pace:

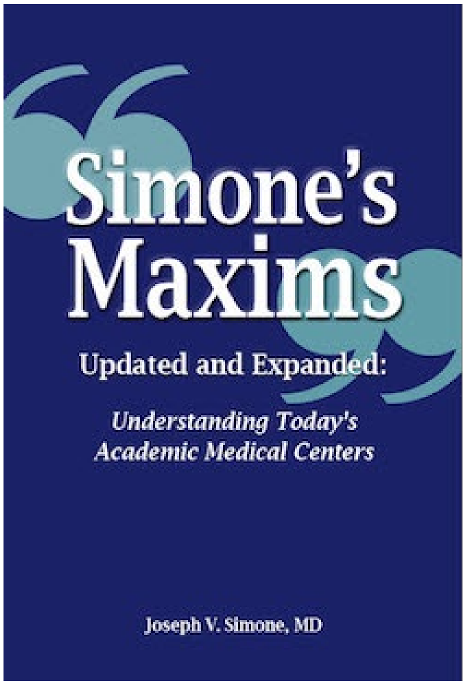
Books



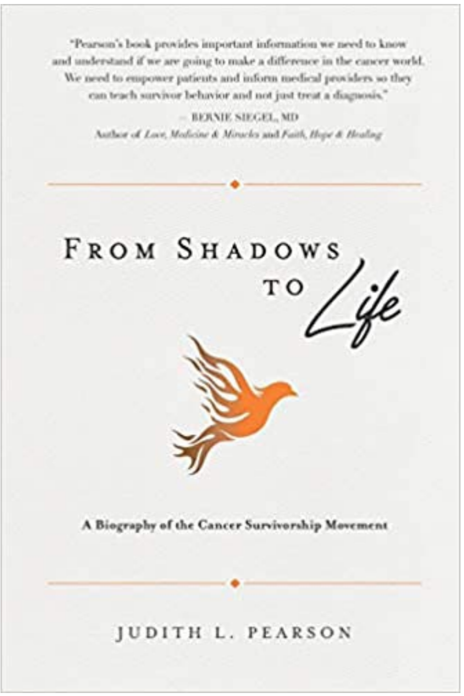
NEW: *Cancer Crusade: The Story of the National Cancer Act of 1971*, by Richard A. Rettig



Stairway of Surprise: A Biography of Kay and Gordon Zubrod, by Charles Gordon Zubrod



Simone's Maxims: Understanding Today's Academic Medical Centers, by Joseph V. Simone



Excerpt: *A Biography of the Cancer Survivorship Movement*: The March, by Judith L. Pearson

The Cancer History Project is looking for out of print or previously unpublished books, and will work with the rights holders to make the book available. Please contact us with suggestions.

Articles

Paul Calabresi: A Founder and Giant in the Field of Medical Oncology
By Cancer Center at Brown University

The Fukushima Daiichi nuclear accident: 10 years later
By Robert Peter Gale

Video: NCCN's Bob Carlson talks about the day he stormed out of a meeting with transplanters
By *The Cancer Letter*

Primary Source: Learning From Disaster: Patient Safety and the Role of Oncology Nurses
By Oncology Nursing Society

Query Theory: A Tribute to Beatrice Mintz, PhD
By Fox Chase Cancer Center

Archives

The Donald Pinkel Archive
In collaboration with his daughter, Mary Pinkel, the Cancer History Project is preserving documents from Donald Pinkel's personal archive.

NCCS Networker, Vol. 1-11 (1987-1997)
The National Coalition for Cancer Survivorship has provided a rich archive of its newsletters: the NCCS Networker, a quarterly publication. Read the first issue: March 1987.

The NCI Oral History Project
A growing collection of oral histories, contributed by NCI.

The Cancer Letter, Vol. 1-40 (1973-2014)
To launch the Cancer History Project, *The Cancer Letter* archive has been made open access for the first time in our 47-year history.

Other ways to explore

Celebrating diversity

- BIPOC Impact: articles about Black, Indigenous, and People of Color oncologists, researchers, and advocates.
- Women in oncology: women who helped shape our field.

Popular topics

- Advocacy
- Bone Marrow Transplant
- Breast Cancer
- Cancer Center
- Childhood Leukemia
- Clinical Trials
- Drug Development
- Founders
- Funding
- Genetics
- Health Disparities
- Hematology
- Immunotherapy
- Leukemia/Lymphoma
- Obituaries
- Oncology Nursing
- Oral History
- Photo archives
- Primary sources
- Radiation Oncology
- Research
- Surgical Oncology
- Survivor Stories
- Videos

This column features the latest posts to the Cancer History Project by our growing list of contributors.

The Cancer History Project is a free, web-based, collaborative resource intended to mark the 50th anniversary of the National Cancer Act and designed to continue in perpetuity. The objective is to assemble a robust collection of historical documents and make them freely available.

Access to the Cancer History Project is open to the public at CancerHistoryProject.com. You can also follow us on Twitter at @CancerHistProj.

Is your institution a contributor to the Cancer History Project? Eligible institutions include cancer centers, advocacy groups, professional societies, pharmaceutical companies, and key organizations in oncology.

To apply to become a contributor, please contact admin@cancerhistoryproject.com.

IN BRIEF

OIG to review FDA's accelerated approval pathway

The Office of Inspector General issued a review of FDA's Accelerated Approval pathway.

The accelerated approval pathway is widely used to approve cancer products.

In a statement announcing the review, OIG said:

> The FDA recently approved Aduhelm (aducanumab) to treat patients with Alzheimer's disease using the accelerated approval pathway."
>
> The accelerated approval pathway allows the FDA to approve drugs that treat serious conditions and that fill an unmet medical need based on a surrogate endpoint, which is a marker that is thought to predict a clinical benefit.
>
> The FDA's approval of Aduhelm raised concerns due to alleged scientific disputes within the FDA, the advisory committee's vote against approval, allegations of an inappropriately close relationship between the FDA and the industry, and the FDA's use of the accelerated approval pathway.
>
> In response to these concerns, we will assess how the FDA implements the accelerated approval pathway. This will include reviewing interactions between the FDA and outside parties as well as other aspects of the process, such as deciding on this pathway and scientific disputes.
>
> We will review the FDA's relevant policies and procedures, determine compliance with them, and make appropriate findings and recommendations based on a sample of drugs approved using the accelerated approval pathway, which will include Aduhelm. We will not assess the scientific appropriateness of the FDA's approval of any of the drugs under review. This work may result in multiple reports.

Jim Gabriele named president and CEO of M2GEN

Jim Gabriele was named president and chief executive officer of M2GEN.

Gabriele is a data scientist who was most recently senior vice president and chief strategy & data science officer within the Medical Devices Sector at Johnson & Johnson.

M2GEN has linked clinical and genomic databases and runs one of the largest observational research studies in cancer, which tracks patients throughout their lifetime, links longitudinal clinical data with molecular information, and enables a deeper understanding of a patient's disease.

As senior vice president and chief strategy & data Science officer at Johnson & Johnson, he led global strategy development, pricing strategy, data science, data strategy, digital customer experience and business insights.

Prior to that, he held senior strategy and data science roles in the Johnson & Johnson Pharmaceutical organization.

Gabriele succeeds Helge Bastian.

Memorial Sloan Kettering establishes MSKCC India

Memorial Sloan Kettering Cancer Center has established MSKCC India to provide cancer patients in India with access to the institution's oncologists, research, clinical trials, and education.

MSKCC India will provide remote opinions via video or written consultations. A Memorial Sloan Kettering Cancer Center oncologist who specializes in a patient's form of cancer will review their medical records, test results, and other materials and provide a comprehensive written opinion, meet with the patient virtually using telemedicine technology, or speak with the patient's local oncologist about their diagnosis and care plan.

In some cases, they may recommend that the patient travel to receive care at Memorial Sloan Kettering Cancer Center in New York City. Specific services include:

- Pathology diagnosis
- Radiology scan reviews
- Next-generation sequencing (MSK-IMPACTTM) of a patient's tumor and treatment recommendations
- Travel assistance to New York City

Memorial Sloan Kettering Cancer Center has partnered with iCliniq, a global telemedicine provider based in India.

MSKCC India will open a physical location in Chennai, centrally located for patients and staff members. This location will serve as a hub for medical staff who will help patients coordinate written or virtual consultations, and they will be able to communicate in English, Hindi, Urdu, Tamil, Telugu and Kannada.

If necessary, employees will be able to collect medical records from patients' homes, making the process more convenient for those utilizing this service. Patients across India will be able to obtain a remote opinion from experts at Memorial Sloan Kettering Cancer Center in the comfort of their home or any internet-enabled location without traveling to MSKCC India in Chennai.

Patients in India now can visit in.mskcc.org/india to learn more about MSKCC India and how to schedule a consultation with a Memorial Sloan Kettering Cancer Center expert.

New software to capture worldwide cancer data

Researchers from Queen's University Belfast, the Northern Ireland Cancer Registry, the International Agency for Research on Cancer and the Union for International Cancer Control have developed CanStaging+, a user-friendly tool aimed at facilitating the recording of comparable cancer staging data worldwide.

The collection of staging data at population-level is currently undertaken by population-based cancer registries. There is a large variation of data collected making it difficult to benchmark and to develop global strategies.

"Almost half of registries in Latin America and the Caribbean (52%) report staging information compared to 96% of registries in North America and Europe," said Anna Gavin, who led the work from the Northern Ireland Cancer registry Centre for Public Health at Queen's University Belfast.

A lack of data and inconsistency is a huge problem in high-income countries too where there were 6-37% of missing staging data for colorectal cancer across seven countries within the International Cancer Benchmarking Partnership between 2010 and 2014.

To mark the launch of the CanStaging+ tool, an accompanying article has been published in *The Lancet Oncology*.

THE CLINICAL CANCER LETTER

CLINICAL ROUNDUP

Keytruda significantly prolonged RFS compared to placebo as adjuvant therapy in phase III KEYNOTE-716 Trial

The phase III KEYNOTE-716 trial investigating Keytruda, Merck's anti-PD-1 therapy, met its primary endpoint of recurrence-free survival for the adjuvant treatment of patients with surgically resected high-risk stage II melanoma.

At an interim analysis, treatment with Keytruda as a single agent showed a statistically significant and clinically meaningful improvement in RFS compared with placebo as adjuvant therapy for these patients.

No new safety signals were observed. These results will be presented at an upcoming medical meeting.

Based on these data, FDA has accepted a new supplemental Biologics License Application for Keytruda for the adjuvant treatment of adult and pediatric (12 years and older) patients with stage IIB or IIC melanoma following complete resection.

The FDA granted the application Priority Review and assigned a Prescription Drug User Fee Act, or target action, date of Dec. 4, 2021.

International collaboration helps refine treatment for childhood leukemia

Scientists at St. Jude Children's Research Hospital are working with colleagues in China to develop better therapy for childhood acute lymphoblastic leukemia.

Results from a large phase III noninferiority clinical trial definitively showed that vincristine and dexamethasone pulses can be eliminated in patients with low-risk disease. The findings were published in *The Lancet Oncology*.

Adding the chemotherapy vincristine plus a steroid (originally prednisone, and later dexamethasone) as pulse therapy for childhood ALL has been part of standard care since the 1970s. This is despite their being associated with neuropsychological side effects, neuropathy and other late effects. However, to date studies about the need for prolonged treatment with pulse therapy have been inconclusive.

"We wanted to study this issue to provide definitive conclusions about whether we can safely omit prolonged pulse therapy with these two drugs to improve quality of life for patients and lessen the burden to their family," said corresponding author Ching-Hon Pui, St. Jude Department of Oncology chair. "That's why doing this study through the Chinese Children's Cancer Group was key: a definitive noninferiority randomized trial of a disease with a high cure rate such as ALL requires very large numbers of patients all treated consistently."

Between January 2015 and February 2019, children with newly diagnosed ALL joined a randomized, open-label, phase III noninferiority study as part of the Chinese Children's Cancer Group ALL-2015 protocol. This clinical trial randomized 6,108 patients, making it the largest clinical trial ever conducted in childhood acute lymphoblastic leukemia.

Patients in continuous remission for one year were stratified and randomized to receive or not receive seven pulses of vincristine plus dexamethasone during the second year of treatment. Using the noninferiority study design, researchers firmly established that pulse therapy can be safely omitted in the second year of care in patients with low-risk disease without affecting their five-year event-free survival or overall survival.

Omitting vincristine plus dexamethasone pulses after the first year of treatment in these children should reduce many acute and late effects of treatment as well as the burden on their families. Additional studies are needed to confirm whether this is true for patients with intermediate or high-risk ALL.

"These findings are very good news for patients and families because shortening this pulse therapy will substantially reduce neuropsychological side effects, emotional disturbances and many other neurological and metabolic late effects," Pui said.

Comprehensive clinical sequencing opens door to the promise of precision medicine

St. Jude Children's Research Hospital investigators have demonstrated that comprehensive genomic sequencing of all pediatric cancer patients is feasible and essential to capitalize on the lifesaving potential of precision medicine.

Results from the St. Jude Genomes for Kids study appear online in the *Cancer Discovery*.

Whole genome and whole exome sequencing of germline DNA was offered to all 309 patients who enrolled in the study. Whole genome, whole exome and RNA sequencing of tumor DNA was carried out for the 253 patients for whom adequate tumor samples were available.

Overall, 86% of patients had at least one clinically significant variation in tumor or germline DNA. Those included variants related to diagnosis, prognosis, therapy or cancer predisposition. Researchers estimated that 1 in 5 patients had clinically relevant mutations that would have gone undetected using standard sequencing methods.

"Some of the most clinically relevant findings were only possible because the study combined whole genome sequencing with whole exome and RNA sequencing," said Jinghui Zhang, , St. Jude Department of Computational Biology chair and co-corresponding author of the study.

Comprehensive clinical sequencing that includes whole genome, whole exome and RNA sequencing is not widely available. But as the technology becomes less expensive and accessible to more patients, researchers said comprehensive sequencing will become an important addition to pediatric cancer care.

"We want to change the thinking in the field," said David Wheeler, St. Jude Precision Genomics team director and a co-author of the study. "We showed the potential to use genomic data at the patient level. Even in common pediatric cancers, every tumor is unique, every patient is unique.

"This study showed the feasibility of identifying tumor vulnerabilities and learning to exploit them to improve patient care," he said.

Tumor sequencing guided the change in treatment for 12 of the 78 study patients for whom standard of care was unsuccessful. In four of the 12 patients, the changes stabilized disease and extended patient lives. Another patient, one with acute myeloid leukemia, went into remission and was cured by blood stem cell transplantation.

"Through the comprehensive genomic testing in this study, we were able to clearly identify tumor variations that could be treated with targeted agents, opening doors for how oncologists manage their patients," said co-corresponding author Kim Nichols, M.D., St. Jude Cancer Predisposition Division director.

Statins may improve survival for triple-negative breast cancer patients

A study led by researchers from MD Anderson Cancer Center found a significant association between cholesterol-lowering drugs commonly known as statins and survival rates of triple-negative breast cancer patients.

Since statins are low in cost, easy to access and produce minimal side effects, this could have an important impact on outcomes for this aggressive disease.

The study, led by Kevin Nead, assistant professor of Epidemiology, was published in *Cancer*. This research extends the current knowledge of the association between statin use and triple-negative breast cancer, and it is the first study that was adequately powered to investigate the association of statins and aggressive breast cancer subtypes.

Researchers found a 58% relative improvement in breast cancer-specific survival and a 30% relative improvement in overall survival with statin use. The median follow-up was 3.3 years for breast cancer-specific survival and 4.4 years for overall survival.

"There is already a body of literature on statins and breast cancer and the results have been inconsistent," Nead said. "Previous research has looked at breast cancer as only one disease, but we know there are many subtypes of breast cancer and we wanted to focus our research on this particularly aggressive form of breast cancer that has limited effective treatment options."

TNBC is an aggressive disease that makes up roughly 10% to 20% of breast cancer diagnoses. Triple-negative means that the breast cancer doesn't have estrogen or progesterone receptors or HER2 positivity, which are the three most common receptors for breast cancer. This combination results in a highly aggressive breast cancer with poor prognosis and limited treatment options since there are few receptors to actively target with existing therapies.

The retrospective study selected patients included in the SEER-Medicare registry and the Texas Cancer Registry-Medicare, two large databases of administrative claims of Medicare-eligible patients. Patients were required to have Medicare Part D prescription coverage to determine their statin use.

The research included data from 23,192 women over age 66 with stage I-III breast cancer. From that patient cohort, 2,281 were incidental statin users, meaning they started a statin within one year following their breast cancer diagnosis. The incidental statin users were 78.1% white, 8.9% Black, 8.4% Hispanic and 4.5% other.

Analysis by breast cancer stage suggested that the association of incidental statin use with improved outcomes may be stronger in women with early stage TNBC. When examining statin intensity, high-intensity statin use had the strongest effect on overall survival among women with TNBC. Researchers also found a statistically significant association between lipophilic statins (L-statin: simvastatin, atorvastatin, lovastatin, fluvastatin, pitavastatin) and improved overall survival.

DRUGS & TARGETS

Opdivo receives EC approval in Esophageal/GEJ indication

The European Commission has approved Opdivo (nivolumab) for the adjuvant treatment of adult patients with esophageal or gastroesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy.

Opdivo is sponsored by Bristol Myers Squibb.

Approval is based on phase III results from the CheckMate -577 trial. Opdivo is now the first and only approved adjuvant therapeutic option in the European Union.

Opdivo also received approval from FDA in May 2021 for the adjuvant treatment of completely resected esophageal or GEJ cancer with residual pathologic disease in patients who have received CRT.

FDA grants Priority Review to Tecentriq as adjuvant treatment in NSCLC indication

FDA has accepted the Biologics License Application and granted Priority Review for Tecentriq (atezolizumab) as adjuvant treatment following surgery and platinum-based chemotherapy for people with non-small cell lung cancer whose tumors express PD-L1≥1%, as determined by an FDA-approved test.

Tecentriq is sponsored by Genentech.

The FDA is reviewing the application under the Real-Time Oncology Review pilot program, which aims to explore a more efficient review process to ensure safe and effective treatments are available to patients as early as possible.

The FDA is expected to make a decision on approval by December 1, 2021.

This application is based on disease-free survival results from an interim analysis of the phase III IMpower010 study, the first and only phase III study of a cancer immunotherapy to demonstrate positive results in the adjuvant lung cancer setting.

The study showed that treatment with Tecentriq following surgery and platinum-based chemotherapy reduced the risk of disease recurrence or death (DFS) by 34% (hazard ratio [HR]=0.66, 95% CI: 0.50-0.88) in people with stage II-IIIA NSCLC whose tumors express PD-L1≥1%, compared with best supportive care.

In this population, median DFS was not yet reached for Tecentriq compared with 35.3 months for BSC. Follow-up on the IMpower010 trial will continue with planned analyses of DFS in the overall intent-to-treat population, including Stage IB patients, which at the time of analysis did not cross the threshold, and overall survival data, which were immature at the time of interim analysis.

Safety data for Tecentriq were consistent with its known safety profile and no new safety signals were identified. Results from the IMpower010 trial were presented at the 2021 ASCO annual meeting.

Cabometyx sNDA receives FDA priority review for previously treated radioactive iodine-refractory differentiated thyroid cancer

A supplemental New Drug Application for Cabometyx (cabozantinib) was granted FDA priority review as a treatment for patients 12 years and older with differentiated thyroid cancer who have progressed following prior therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate).

Cabometyx is sponsored by Exelixis Inc.

The FDA granted Priority Review designation and assigned a Prescription Drug User Fee Act target action date of Dec. 4, 2021.

The sNDA is based on the results of COSMIC-311, a phase III pivotal trial evaluating Cabometyx versus placebo in patients with radioactive iodine-refractory DTC who progressed after up to two prior vascular endothelial growth factor receptor (VEGFR)-targeted therapies.

At a planned interim analysis, Cabometyx met one of the trial's primary endpoints, demonstrating a significant improvement in progression-free survival versus placebo.

In February 2021, the FDA granted Breakthrough Therapy Designation to Cabometyx as a potential treatment for patients with DTC that has progressed following prior therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate) based on these results. Detailed study findings were presented at the 2021 American Society of Clinical Oncology annual meeting and were published by *The Lancet Oncology* in July 2021.

BMS issues statement on Istodax relapsed/refractory peripheral T-cell lymphoma U.S. indication

Bristol Myers Squibb has withdrawn the U.S. indication for Istodax for relapsed/refractory peripheral T-cell lymphoma.

Istodax was approved under the accelerated approval pathway, but failed to meet the efficacy endpoint in a confirmatory trial.

A statement by BMS follows:

> In 2011, Celgene Corporation, now a wholly owned subsidiary of Bristol Myers Squibb, received accelerated approval by the U.S. Food & Drug Administration for Istodax (romidepsin), a histone deacetylase inhibitor, as monotherapy for the treatment of peripheral T-cell lymphoma in adult patients who have received at least one prior therapy.
>
> This accelerated approval was based upon results from two clinical studies, assessing the effect of Istodax on the surrogate endpoint of overall response rate. Bristol Myers Squibb conducted a subsequent confirmatory phase III study evaluating romidepsin plus CHOP (Ro-CHOP) versus CHOP in first-line PTCL patients, but the trial did not meet the primary efficacy endpoint of progression free survival.
>
> Based on this outcome, Bristol Myers Squibb made the decision to withdraw the PTCL indication from the U.S. market. The company took this action in accordance with the FDA's requirements for evaluating accelerated approvals that have not demonstrated sufficient clinical benefit.
>
> Bristol Myers Squibb is notifying healthcare professionals about the withdrawal. Istodax remains on the market for treatment of patients with cutaneous T-cell lymphoma (CTCL) who have received at least one prior systemic therapy. Patients who are being treated with Istodax for PTCL should consult with their healthcare provider in all aspects of their medical care and may remain on treatment if deemed clinically appropriate by the treating physician. For patients who are currently being treated with Istodax for PTCL, and who have questions about access and reimbursement support, please contact BMS Access Support at 1-800-861-0048 or visit www.bmsaccesssupport.com.
>
> While the outcome of the confirmatory study in peripheral T-cell lymphoma is disappointing, Bristol Myers Squibb will continue to provide Istodax for patients with cutaneous T-cell lymphoma, where it remains an approved and important treatment option," said Noah Berkowitz, M.D., Ph.D., senior vice president, Hematology Development, Bristol Myers Squibb. "As always, our efforts across blood cancer research and development remain centered on delivering better outcomes for patients in need.
>
> Since the initial approval of Istodax, nearly a decade ago, more options have been made available for patients, many of which have redefined treatment across PTCL and other hematologic conditions.

NCI TRIALS

NCI Trials for August 2021

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

For further information, contact the principal investigator listed.

Phase I - 10363
A Phase I Study of Pomalidomide and Nivolumab in Patients with Virus-Associated Malignancies with or Without HIV

NCI Center for Cancer Research
Lurain, Kathryn
(301) 250-5156

Phase I/II - 10417
Clinical Evaluation of ASTX727 in Combination with Venetoclax All-Oral Therapy vs Standard of Care Cytarabine and Anthracycline Induction Chemotherapy for Younger FLT3WT Patients with ELN High- Risk Acute Myeloid Leukemia

Yale University Cancer Center LAO
Savona, Michael Robert
(615) 936-3321

Phase I/II - 10428
A Phase I/II Study of Abemaciclib in Patients with HIV-Associated and HIV-Negative Kaposi Sarcoma

NCI Center for Cancer Research
Ramaswami, Ramya
(301) 451-9018

Phase II - NRG-BN010
A Safety Run-In and Phase II Study Evaluating the Efficacy, Safety, and Impact on the Tumor Microenvironment of the Combination of Tocilizumab, Atezolizumab, and Fractionated Stereotactic Radiotherapy in Recurrent Glioblastoma

NRG Oncology
Bagley, Stephen Joseph
(215) 614-1858

Phase III - URCC-19178
Optimizing Functional Outcomes of Older Cancer Survivors After Chemotherapy

University of Rochester NCORP Research Base
Mohile, Supriya Gupta
(585) 275-9319

Phase Pilot - AMC-111
Impact of Behavior Modification Interventions and Lung Cancer Screening on Smoking Cessation in People Living with HIV: A Feasibility Study

AIDS Malignancy Consortium
Sigel, Keith Magnus
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