THE CANCER LETTER

Jan. 8, 2016 • www.cancerletter.com • Vol. 42 No. 1

From a 2008 video produced by NCCS titled "Ellen Stovall: One Person Can Make a Difference." The video is available here.

Ellen Stovall, Pioneering Advocate For Survivorship, Dies at 69

By Paul Goldberg

Ellen Stovall, one of the most respected and knowledgeable cancer advocates in Washington, died Jan. 5.

The cause of death was a heart attack.

Stovall, 69, was first diagnosed with Hodgkin's lymphoma in 1971. Her disease recurred in 1983. In 2007, she had bilateral mastectomies due to the late effects of the radiation treatment. Her heart disease and chronic pain were also attributed to her original treatment.

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Nobel Laureate Alfred Gilman, Defender of Good Science, Dies at 74

By Paul Goldberg

Alfred G. Gilman, a Nobel laureate who concluded his academic career in the role of chief scientific officer of the Cancer Prevention and Research Institute of Texas, died Dec. 23, 2015. Gilman, 74, had pancreatic cancer.

Gilman shared the 1994 Nobel Prize in Physiology or Medicine with Martin Rodbell of the National Institute of Environmental Health Sciences for their discovery of G proteins—guanine nucleotide-binding regulatory proteins. G proteins are central to signaling transduction, the process of receiving signals from outside the cell and activating a range of cellular responses.

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Cancer Death Rate Continues Steady Drop

Steady reductions in smoking combined with advances in cancer prevention, early detection, and treatment have resulted in a 23 percent drop in the cancer death rate since its peak in 1991, according to the annual Cancer Statistics report from the American Cancer Society.

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Advocate Ellen Stovall, 69, Dies From Heart Attack

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"Ellen is a rare transformational figure in cancer care, who saw an enormous unfilled need and led the development of the entire concept of cancer survivorship," said Norman Coleman, head of the Experimental Therapeutics Section and associate director of the NCI Division of Cancer Treatment and Diagnosis, and senior medical advisor at the HHS Office of the Assistant Secretary for Preparedness and Response.

"She recognized her good fortune to have been diagnosed with Hodgkin's disease early in the curative era, built on accomplishments from the brilliance of Henry Kaplan, Saul Rosenberg, Vince DeVita and the NCI team, Gianni Bonadonna and others. Despite all the difficulties that resulted from her treatment, she was always grateful for being alive."

Stovall's advocacy was focused primarily on survivorship issues, but her expertise encompassed the entire landscape of cancer: basic science, translational research, trial design, drug approval criteria, drug pricing, and payment policy.

She worked at the National Coalition for Cancer Survivorship since 1992. When she was in her thirties and forties, she told friends that because of the delayed effects of her treatment, she didn't expect to live deep into her fifties.

"I don't want to write about Ellen's numerous awards, where she went to school, what committees she sat on. I want to write about Ellen. Because no matter what table she sat at or degree she held or plaque she was given, she wanted to cut through all the BS and do two things: help people and get the right things done," Fran Visco, president of the National Breast Cancer Coalition, said in an email.

There was no way to distinguish Ellen-the-friend from Ellen-the-insider. Whether you were an advocate, reporter, an NCI director or an FDA commissioner, Stovall was someone you called when you wanted to find out what's really going on and what to do about it.

Stovall's ability to stay on top of science and policy was remarkable, but there was more to her.

Like the arrow of a compass, her opinion pointed to the highest moral mark. If you were misreading the situation or were full of crap, she could be counted on to tell you. Her unbreakable loyalty to friends, her sense of humor, and her willingness to stay on the phone and take an already meandering conversation for that extra loop were an added bonus. And another thing: in a city that blabs, Stovall didn't.

"I first met Ellen shortly after the National Breast Cancer Coalition was formed," said Visco. "Pam Onder, on behalf of NCCS and with Ellen's blessing, was part of the launch of NBCC and a member of our first board. Pam was amazing. And then I was introduced to Ellen.

"I don't think I have ever known anyone like her. She and I bonded immediately, probably in large part due to our concern about advocacy becoming co-opted by every other stakeholder, a topic we discussed many times over the years. And then there was our uncanny ability to roll our eyes at the same thing at the same time. There are many, many egos in cancer advocacy. Ellen's wasn't one of them. I saw her time and time again step aside and let someone else take the mike.

"When a controversial, difficult issue arose in the cancer community, which happened pretty much every day, she would bring all sides together to discuss it. She truly believed that somehow everyone would ultimately work for the better good. She had real integrity. Ellen had this amazing ability to challenge everyone and still maintain their utmost respect and love.

"I am not sure Ellen would like that last part. I think she really wanted to be feared more than loved. But she got a lot more done for all of us through her approach. And she did instill fear in all of us the fear of disappointing her. She was so very smart. And funny. And courageous. I was incredibly honored when she asked me to present the award when she was feted by NCCS on her 'retirement.' (Which I don't think ever really happened, thankfully.)

"Her board leadership at the time was a bit concerned and asked to see my remarks ahead of time. I

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Editorial, Subscriptions and Customer Service:
202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016
General Information: www.cancerletter.com

Subscription $405 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc.

intended to talk about how Ellen was smart and strong and had one of the qualities I treasure the most: she could be a strategic bitch and loveable at the same time.

"They asked me to remove the last part. I did. When I told Ellen, she laughed, and when she thanked me on stage for my remarks, in front of the hundreds of people gathered to honor her, luminaries in the cancer world, she spoke about how she valued the fact that we were two cancer bitches.

"Ellen Stovall, advocate extraordinaire. *Cojones magnifico*!"

A Truth Teller

Stovall was the NCCS president and CEO, but in recent years she served as the organization's senior health policy advisor.

"I first met Ellen Stovall when I arrived in Washington in 1999," said Richard Pazdur, director of the FDA Office of Hematology and Oncology Drug Products. "I was always impressed with the honesty and clarity she brought to any conversation on cancer.

"She was 'the patient voice' before we coined the term. Many times we—those in government, academics, industry or patient care—get lost in the daily grind and forget the reason we are all here is the patient. Ellen always brought us back to that patient focus.

"FDA had worked with and NCCS on many projects, including the use of novel endpoints in clinical trials and expanded access. Ellen was there for the larger cancer community issues, but was also present for the individual patient. My late wife, Mary, and Ellen formed an enduring partnership in the last months of their lives since both of them realized a dire prognosis and shared a mutual support and kinship that only those in that situation can understand."

Stovall's wisdom was in demand for more than a quarter century.

"Ellen was, above all else, a friend. What was unusual and wonderful about Ellen is that she was an instant friend as well as a deep friend," said Richard Klausner, a former NCI director who is now the senior vice president and chief opportunity officer of Illumina Corp., and founder and director of Juno Therapeutics.

"She was a truth teller, and there was no editing when Ellen and I talked. I met her soon after I became NCI director, and she was a guide, an advisor and a teacher. She came to every meeting with a spirit of generosity that demanded reciprocation. That's how the Office of Cancer Survivorship at the NCI was formed and along with it a commitment to survivorship research.

"Her death is a shock, because she was always so alive bringing life and even humor to the most serious issues without ever diminishing their import. She will be missed."

Harold Varmus sought Stovall's advice, too.

"For nearly twenty years I have benefited from Ellen Stovall's wise counsel about many aspects of cancer—from the aspirations of advocates for the advances science promises to the sufferings of patients living with the disease," former NCI Director Varmus said in an email. "One of Ellen's remarkable qualities was her temperament: she was able to deliver all kinds of news and convey clear opinions with dignity, clarity, intelligence, and good humor.

"All of us who advocate for medical research and better health care have lost an inspiring leader."

NCI Acting Director Doug Lowy said that Stovall moved those at the institute to do their best work.

"I speak for many at NCI when I say we will miss Ellen Stovall, ever the stalwart advocate for cancer patients," Lowy said. "Ellen was a pioneer who shaped the fields of cancer survivorship and cancer policy. She was a longtime friend of the Institute—a friend who pushed us all to do better. We will carry her voice in our heads and our hearts and her commitment to cancer patients will continue."

Otis Brawley first met Stovall in 1991, soon after he finished his fellowship at NCI and stayed on at the Division of Cancer Prevention and Control.

"Ellen was my dear friend, supporter and mentor for more than 25 years," said Brawley, chief medical officer of the American Cancer Society. "She had a moral compass and wisdom rarely seen. Her influence on and encouragement of scientists, physicians, corporate executives, politicians, and patients was incredible. She taught us to always remember the human being with cancer.

"It was Ellen who defined the term 'cancer survivor' as someone who has been diagnosed. Her actual quote is 'You are a survivor from the moment you are told you have cancer.'"

Advocate and Insider

Coleman met Stovall while working on Cancer at the Crossroads: A Report to Congress for the Nation (Subcommittee to Evaluate the National Cancer Program, 1994), where Stovall represented the newly emerging survivorship community.

"It was this report under the leadership of Paul Calabresi, the inspiration of Harold Freeman, chair of the President's Cancer Panel, and the extraordinary organizational ability of Cherie Nichols that proposed the strategic sequence of patients, translational research

and basic research that raised the value and emphasized the essential links among all aspects of cancer care and research—with patients first," Coleman said.

"Ellen is an example of the good that comes about, not necessarily from technical experts, academics or politicians, but from people who see a need and who work to fill it for the good of others. Her legacy is assured as the world of cancer care reflects her contributions," Coleman said.

"She would undoubtedly be embarrassed by the accolades and her focus would be on filling the needs for cancer care and research. She would expect nothing less of us to do our best and expand the effort for quality care, application of advances to all people and accelerating progress through research."

Stovall helped define the field of survivorship.

"Ellen was truly a legend in cancer advocacy. She and her colleagues and collaborators at NCCS pioneered the concept of survivorship," said Shelley Fuld Nasso, NCCS CEO. "She touched thousands of lives, personally and through her advocacy. She believed in helping cancer survivors live as well as they can, for as long as they can. And she did exactly that in her own life, even if it was shorter than we would all have hoped. It has been a privilege to work with her for the last several years, and I am honored to carry on her legacy at NCCS."

Stovall grew up in Honesdale, Pa., a small town near Scranton. Her father, Nathan Lewis, served as a captain in the U.S. Army, where he was involved in hospital administration during World War II. After serving in the Army, Nathan came home to Honesdale, where he and his wife's brother, Bill Roos, ran Katz Department Store, circa 1871-1984.

Nathan and his wife, Edna, raised Ellen and her younger brother, Steve.

Ellen attended Penn State University, where she studied journalism. There she met John Stovall, a native of Washington, D.C. After college, she married John and they moved to Gaithersburg, Md.

At 24, six weeks after giving birth to their son Jonathan, Ellen was diagnosed with Hodgkins' lymphoma. She began treatment on the day the National Cancer Act was signed by President Richard Nixon, on Dec. 23, 1971. Following treatment, Ellen started the first cancer peer support group for young adults in Washington, at Georgetown University Hospital.

"Many cancer survivors who experienced the degree of radiation that was a common treatment protocol for Hodgkin's lymphoma at the time of Ellen's original diagnosis in 1973, have a high risk for morbidity from an open heart procedure many years after treatment," shared Nina Wendling, former colleague at NCCS and current chief operating officer with the International Cancer Expert Corps.

Stovall learned about NCCS during a recurrence of her cancer, through a pamphlet in a psychiatrist's office. In an interview in 2009, at the time she was honored as one of 10 Women to Watch by Jewish Women International, Stovall said that the word "survivor" in the NCCS pamphlet caught her attention. She was empowered by the concept of being a survivor instead of being a "victim," the term that had been applied to her up to that time.

Stovall was elected to the NCCS board of directors in 1988 and was named the organization's president and CEO in 1992. She identified passion as her core qualification for the job and admitted that managing an organization was not her strongest skill. In addition to passion, Stovall brought to the job the ability to articulate the challenges and triumphs of cancer survivorship, connect with other cancer survivors, and convene coalitions and organizations. She was also a master at persuading others to dedicate time and resources to the pursuit of solutions for the problems faced by cancer survivors.

In 1993, Stovall encouraged the leaders of a few cancer organizations to collaborate in cancer policy advocacy. The result of that collaboration is the Cancer Leadership Council, a network of approximately 30 organizations cooperating in public policy activities. She also fostered an alliance between NCCS and the American Society of Clinical Oncology that resulted in a 28-organization collaborative focusing on the development, sharing, and implementation of cancer quality measures, tools, and practical programs in cancer practice.

She was a founding member of the Institute of Medicine's National Cancer Policy Board and its successor, the National Cancer Policy Forum. These organizations brought together government officials, pharmaceutical industry representatives, academics, health professionals, and patient advocates for years of work that defined the health care, personal, and professional issues confronted by cancer survivors; identified the strengths and weaknesses of the cancer care system; and described a system of care for the "whole patient."

The health care system and policy recommendations in these groundbreaking reports are still considered a map for reform of the cancer care system. Chief among these was the 2006 report, which Stovall co-edited, titled From Cancer Patient to Cancer Survivor: Lost in Transition.

This volume chronicled the challenges encountered by cancer survivors and their families after curative treatment ends, and potential pathways to address these. The report has served for the past decade as the definitive roadmap for survivorship research and care.

Under Stovall's leadership, NCCS in 1998 launched "The March – Coming Together to Conquer Cancer," a gathering of 250,000 people on the National Mall and a million more in grassroots events nationwide. The march's agenda focused on increasing federal funding for cancer research and improving cancer care quality, and was credited with influencing a congressional decision to dramatically boost cancer research funding.

In addition to the march, one of Stovall's most important contributions to cancer survivorship was her articulate and compelling advocacy for more research conducted by NCI on the long-term impact of surviving cancer.

In the wake of the very first National Congress on Survivorship held in Washington in November 1995, Stovall took the Imperatives for Quality Cancer Care document prepared for the congress to then-NCI Director Klausner, who would then establish the Office of Cancer Survivorship at NCI to drive the science needed to understand and meet the unique needs of the growing population of those living with, through and beyond cancer—a number that now encompasses 15.5 million Americans.

During the years of Stovall's leadership, NCCS distributed more than a half million Cancer Survival Toolboxes, an informational tool to help cancer patients navigate their cancer care, and developed and distributed other educational materials for cancer survivors. The organization also pursued an aggressive public policy and advocacy program that achieved reforms of the Medicare program to enhance cancer care quality, encouraged reorganization of cancer drug review at the FDA, and guaranteed third-party coverage for health care costs for individuals participating in clinical trials.

Stovall represented cancer survivors and articulated patient concerns during a six-year term on the NCI's National Cancer Advisory Board, a position she was appointed to by President Bill Clinton. She also served as a board member of The Leapfrog Group, a board member of the National Committee on Quality Assurance, and as a member of committees of the Robert Wood Johnson Foundation, which focused on improving health care quality.

In 2013, Stovall participated in a clinical trial to replace a calcified aortic valve via a percutaneous procedure.

"As a strong advocate for clinical research coupled with her desire to have a better quality of life, Ellen had the procedure performed at the Washington Hospital Center," said Wendling. "It is the kind of technology that Ellen and others like her, who as long-term survivors from radiation therapy, can now benefit.

"She waited for seven years for the procedure to be available and was ever grateful she was able to take advantage of the evolving science."

Services will be held Sunday, Jan. 10, at 1 p.m. at Congregation Beth Israel in Honesdale, Pa. Interment will be at Beth Israel at Dyberry Cemetery in Honesdale.

The family will be receiving friends Tuesday, Jan. 12, from 4-9 p.m. at home, 11430 Flints Grove Lane, Gaithersburg, Md. NCCS will host a tribute in Washington in the coming weeks. Details will be announced soon.

In lieu of flowers, donations may be made to: Congregation Beth Israel, 615 Court Street, Honesdale, PA 18431, or the National Coalition for Cancer Survivorship, at 1010 Wayne Ave, Suite 315, Silver Spring, MD 20910.

Nobel Laureate Alfred Gilman, Of UT Southwestern, Dies at 74

(Continued from page 1)

G proteins are found in nearly all cells, and are central to body processes that include vision, smell, hormone secretion, and thinking in humans. Problems in G-protein signaling contribute to a range of diseases, including cholera, whooping cough, and cancer.

At UT Southwestern, Gilman served as chairman of pharmacology and dean of the medical school. He was also a former executive vice president for academic affairs and provost at UT Southwestern Medical Center.

In addition to being an academic luminary, Gilman was an exceptional teacher. Once, in 1973, while teaching a pharmacology class at the University of Virginia, Gilman threw out a question: "How do drugs work?"

One student, Leonard Schleifer, had the answer: They work through receptors on the surface of cells.

"Al then reached behind the auditorium lectern, took out a six-pack of Budweiser, and threw it at me," Schleifer recalled in a conversation recently. "That started a 40-year friendship."

Later, Gilman encouraged Schleifer to change his academic focus from MD to MD and PhD, and later still he mentored the younger man as he founded Regeneron Pharmaceuticals Inc.—where Gilman served as a co-founder and a board member.

Speaking with this reporter, Schleifer was having difficulty switching to past tense when talking about Gilman. "He has an extreme, if not exaggerated, sense of right and wrong, good and evil, fair and unfair, and when he sees the wrong side of these equations, he cannot sit idly by," said Schleifer. "Al says what he believes is right and fervently follows that path."

At CPRIT, a Texas taxpayer-funded institution that spends $300 million a year on cancer research and other cancer-related endeavors, Gilman developed what scientists describe as one of the finest peer review system in existence.

When politicians tried to interfere with the manner in which CPRIT funds were allocated, Gilman resigned. In a spectacular display of solidarity, scientists who were involved in CPRIT's peer review walked out as well.

A year before his death, Gilman provided a detailed account of his battle to protect public money from what he described as an arrogantly conceived, sloppily executed incursion.

In the upcoming weeks, starting with next week's issue, The Cancer Letter will run a series of stories that re-examine the CPRIT controversy based on Gilman's account of his decision to become a whistleblower. The stories of the ungluing of CPRIT and controversies at MD Anderson Cancer Center developed concurrently, and while some of these events have been described in The Cancer Letter before, the series will present this material systematically, with the benefit of historical perspective—and Gilman's insight.

Gilman took the CPRIT job in 2009. He resigned three years later, bringing attention to the scandal that would otherwise have gone unnoticed.

An argument can be made that Gilman's very public departure in 2012 created an obligation for his successor at CPRIT to recreate the premier peer review system Gilman put together.

"Whatever CPRIT has managed to accomplish is directly attributable to Al's vision for the program," said Margaret Kripke, his successor as the scientific director. "Basically, the program is the one Al set up initially, and I don't see that changing in the near future."

Named After a Medical Text

"Dr. Gilman was a giant in medical research. His discovery of G proteins and their critical functions is a cornerstone of research across virtually every important domain of medicine," said Daniel Podolsky, president of UT Southwestern Medical Center, said in a statement. "As a scientist, teacher, and leader, Dr. Gilman's contributions are legion. He mentored many scientists who have gone on to become leaders in their fields, and his dedication to serving UT Southwestern was unwavering."

Alfred Gilman

Gilman served as chairman of pharmacology at UT Southwestern for more than two decades. He retired from the Medical Center in 2009 as a regental professor emeritus to assume the position of chief scientific officer of CPRIT, a position he held until 2012.

On Dec. 4, 2014, the UT System Board of Regents approved the creation of the Alfred G. Gilman Distinguished Chair in Pharmacology, which supports the chairman of the Department of Pharmacology and efforts in pharmacology. The endowment, totaling $1 million, was made possible by a variety of donors, and the inaugural holder of the chair is David Mangelsdorf, chairman of pharmacology at UT Southwestern, who was Gilman's successor in the department.

In 2012, Gilman became the first UT Southwestern Nobel laureate to donate his medal to the Perot Museum of Nature and Science, saying it gave him enormous pleasure to think that it might inspire a new generation of scientists.

Gilman was born July 1, 1941, in New Haven, Conn., the son of the renowned pharmacologist Alfred Gilman, who was on the faculty at Yale University and who, along with Louis Goodman, authored the preeminent

textbook *The Pharmacological Basis of Therapeutics.*

The elder Gilman chose his son's middle name, Goodman, in honor of Dr. Goodman. Gilman often said that he was named after a textbook. He became the editor of multiple editions of that textbook from 1980 to 1990.

The younger Dr. Gilman received his bachelor of science *summa cum laude* in biochemistry from Yale in 1962, followed by his M.D. and doctorate degree in pharmacology in 1969 from Case Western Reserve University. He completed his postdoctoral training in the Laboratory of Biochemical Genetics at NIH (1969 to 1971). From there, he went to the University of Virginia, where he discovered G proteins in 1977.

In 1981, he became chairman of pharmacology at UT Southwestern, where he continued to characterize G proteins. His observations provided the first firm molecular basis for understanding certain signal transduction processes present throughout nature.

"In 1981, Al Gilman became our neighbor in a nearby lab on the fifth floor. We immediately became friends because of several shared passions, particularly for hard core science. Of all the scientists I have known, Al had the most unrelenting commitment to scientific integrity. He could not abide sloppy or phony science, and he said so openly, even when it would have been much safer to stay silent. We may never see the like of him again," Nobel Laureate Michael Brown, regental professor of the UT System, director of the Erik Jonsson Center for Research in Molecular Genetics and Human Disease, said in a statement.

The UT System Board of Regents named Gilman a Regental Professor in 1995.

In 2004, Gilman became director of a new research center at UT Southwestern—the Cecil H. and Ida Green Comprehensive Center for Molecular, Computational and Systems Biology—devoted to a new field he described as working "to begin to understand how all the 'parts' of cells—genes, proteins, and many other molecules—work together to create complex living organisms." That same year, he was named dean of UT Southwestern Medical School. In 2006, he added the title of executive vice president for academic affairs and provost of UT Southwestern.

Along with the Nobel Prize, his many honors included election to the National Academy of Sciences (1985), winning the Lasker Basic Medical Research Award (1989), and an honorary doctor of medicine from Yale University (1997).

Immediate survivors include wife Kathryn; daughters, Amy Ariagno and Anne Sincovec; and son, Edward Gilman.

National Cancer Death Rate Continues Steady Drop

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The drop translates to more than 1.7 million cancer deaths averted through 2012. The findings were published in CA: A Cancer Journal for Clinicians. The report estimates there will be 1,685,210 new cancer cases and 595,690 cancer deaths in the United States in 2016.

Overall cancer incidence is stable in women, and declining by 3.1 percent per year in men, from 2009-2012, with one-half of the drop in men due to recent rapid declines in prostate cancer diagnoses as PSA testing decreases.

Cancer mortality continues to decline. Over the past decade of data, the rate dropped by 1.8 percent per year in men and 1.4 percent per year in women. The decline in cancer death rates over the past two decades is driven by continued decreases in death rates for the four major cancer sites: lung, breast, prostate, and colon/rectum.

Death rates for female breast cancer have declined 36 percent from peak rates in 1989, while deaths from prostate and colorectal cancers have each dropped about 50 percent from their peak, a result of improvements in early detection and treatment. Lung cancer death rates declined 38 percent between 1990 and 2012 among males and 13 percent between 2002 and 2012 among females due to reduced tobacco use.

The report also features an analysis of leading causes of death by state and finds that, even as cancer remains the second leading cause of death nationwide, steep drops in deaths from heart disease have made cancer the leading cause of death in 21 states: Alaska, Arizona, Colorado, Delaware, Florida, Georgia, Idaho, Kansas, Maine, Massachusetts, Minnesota, Montana, Nebraska, New Hampshire, New Mexico, North Carolina, Oregon, South Carolina, Vermont, Virginia and Washington.

In addition, cancer is the leading cause of death among adults ages 40 to 79, and among both Hispanics and Asian/Pacific Islanders, who together make up one-quarter of the U.S. population. Heart disease remains the top cause of death overall in the United States. In 2012, there were 599,711 deaths from heart disease, compared to 582,623 deaths from cancer.

"We're gratified to see cancer death rates continuing to drop. But the fact that cancer is nonetheless becoming the top cause of death in many populations is a strong reminder that the fight is not

over," said Otis Brawley, chief medical officer of the American Cancer Society.

Other findings from the report include:

• Among children and adolescents, brain cancer has surpassed leukemia as the leading cause of cancer death, a result of more rapid therapeutic advances against leukemia.

• Thyroid cancer continues to be the most rapidly increasing cancer (>5 percent per year in both men and women), partially due to overdiagnosis because of the increased use of advanced imaging techniques.

• Colorectal cancer incidence and death rates declined by about 3 percent per year in both men and women from 2003 through 2012, with momentum gaining in the most recent years. However, rates increased by 1.8 percent per year from 1992 through 2012 in men and women aged younger than 50 years, among whom screening is not recommended for those at average risk.

• In contrast to stable or declining trends for most cancers, incidence rates increased from 2003 to 2012 among both men and women for some leukemia subtypes and for cancers of the tongue, tonsil, small intestine, liver, pancreas, kidney, renal pelvis, and thyroid.

• In addition, incidence rates increased in men for melanoma; myeloma; and cancers of the breast, testis, and oropharynx. Among women, incidence rates increased for cancers of the anus, vulva, and uterine corpus.

• Recent declines in incidence for melanoma and liver cancer among young adults may portend a reduction in the burden of these cancers in future generations.

• Death rates from cancer have dropped from a peak of 215.1 per 100,000 in 1991 to 166.4 in 2012. The decline is larger in men (28 percent since 1990) than in women (19 percent since 1991).

• Breast cancer is the leading cause of cancer death in women aged 20 to 59 years, while lung cancer is the cause of cancer death in women 60 and older. Among men, leukemia is the leading cause of cancer death for those aged 20 to 39 years, whereas lung cancer ranks first among men 40 and older.

Incidence data comes from the NCI Surveillance, Epidemiology, and End Results program, the Centers for Disease Control and Prevention National Program of Cancer Registries, and the North American Association of Central Cancer Registries. Mortality data comes from the National Center for Health Statistics.

Lab-Developed Tests

AMP Responds to FDA Report On Regulation and Oversight

By Conor Hale

The Association for Molecular Pathology responded to the FDA's call for oversight of laboratory developed tests, rebutting 20 case studies published by the federal agency that illustrated possible harms inflicted on patients when laboratories did not follow FDA requirements.

The AMP said the agency's collection of case studies "grossly misrepresents the public health concerns of laboratory developed testing procedures," and said that FDA oversight would likely prevent few of the potential patient harms.

In the case of clinical trials performed at Duke University using a faulty genomics predictor to assign cancer treatment to individual patients, the AMP said that that test did not cause patient harm, and was not used in a clinical setting.

Ahead of a congressional hearing on the role of the FDA in November, the agency offered warnings of the dangers of marketing tests without proven clinical validity, and listed the possible harms from false positive and false negative results. (The Cancer Letter, Nov. 20.)

The AMP said that asking academic medical centers, hospitals and health systems, and cancer center laboratories to submit lab-developed tests to FDA for pre-introduction approval would be financially and administratively infeasible. "Any such service for which FDA-clearance or approval is required will very likely cease to be offered, and patients will lose access to innovative and accurate laboratory testing procedures," the association said.

"The 20 tests described by FDA are mostly a hodgepodge of outlier assays including tests that were never offered, tests for which comparable FDA assays perform poorly, tests for poorly defined disorders with psychologic components, and use of an FDA-approved test off-label," said Roger Klein, professional relations chair of the AMP. "Also included are examples of tests that are widely regarded as major scientific breakthroughs and which are recommended in major medical guidelines."

The association said that the CLIA program, run by the Centers for Medicare and Medicaid Services, would be a better choice than the FDA for addressing the problems posed by laboratory developed tests. The CLIA program covers approximately 251,000

laboratory entities, according to CMS.

"AMP believes that the most reasonable and effective path forward is for Congress to insist that the CLIA program modernize, expand its current network of third party medical experts, and utilize scientific expertise from FDA and CDC rather than relinquishing its duties regarding the accuracy and reliability of [laboratory-developed testing procedures, or LDPs]," said AMP President Charles Hill.

"AMP strongly urges the Department of Health and Human Service [sic] and the Office of Management and Budget to perform a thorough, scientifically unbiased analysis of potential harms and benefits of FDA regulation of LDPs prior to embarking on a massive new regulatory program that would be enormously disruptive to health care and would likely have profound adverse consequences for patients across the country."

The AMP report, published Dec. 13, is titled: "Facts FDA Ignored: An analysis of the FDA report, 'The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies.'"

The association's report said that, in some of the FDA's examples, the patient harms stemmed from issues that would not be solved with FDA oversight, such as problems "with treating physicians using treatments outside accepted medical practice," or "failure of treating physicians to follow up a screening test with a diagnostic confirmation test."

In the FDA's specific example regarding genomic assays used in three clinical trials at Duke University, the AMP said that the "test was not offered in a clinical setting and did not cause patient harm," even though the assays were directly used to assign patients to specific cancer treatments, on the claim that the tests could predict an individual patient's response.

One patient in the Duke trials, breast cancer survivor Joyce Shoffner, spoke with The Cancer Letter, detailing the biopsy procedures she underwent and the side effects of her subsequently assigned chemotherapy treatment. Altogether, 117 patients were enrolled in the Duke trials (The Cancer Letter, May 22).

The case of the faulty predictors used in the trials led to an investigation conducted by the Institute of Medicine—and the retraction of scientific papers in Nature Medicine, the Journal of Clinical Oncology, and the New England Journal of Medicine, among others, totaling 27 complete or partial retractions, according to the FDA's report.

In court, attorneys for Duke also stated that no patients were harmed in its clinical trials.

"Plaintiffs cannot show that a different course of treatment would have made any difference in their care or chance of survival," reads a motion filed by the university's attorneys in January. "Expert testimony in this case has not established that any clinical trial available in the United States in 2010 would have prolonged plaintiffs' life expectancy or treated them more effectively. Therefore, plaintiffs cannot meet causation of damage elements of their negligence per se claim." (The Cancer Letter, Jan. 23.)

The AMP said that FDA ignored certain facts in its report when citing the Duke case, namely that "the controversies surrounding the clinical trials in question resulted from investigator misconduct and data falsification involving this NIH-supported research," and not due to the performance of a laboratory-developed test itself.

"The trials were initially suspended and then permanently stopped in 2010. Interestingly, FDA reviewed one of the studies in 2009, several years after its initiation, and concluded that the study would require an Investigational New Drug application, which had not been submitted," the AMP report said.

"An FDA audit in 2011 further showed that an Investigational Device Exemption application had not been filed, but otherwise found no significant deficiencies in Duke's Institutional Review Board conduct. FDA oversight of LDPs is unlikely to have solved problems of research data falsification and investigator misconduct."

The AMP's conclusion was that the test was not offered in a clinical setting and did not cause patient harm, and that FDA review "would not uncover scientific misconduct and data falsification within a broader research study."

Regarding the report produced by the Institute of Medicine in the aftermath of the Duke controversy, the FDA report said: "In the IOM's assessment, greater FDA oversight and involvement may have uncovered errors and validation issues before the test was used in clinical trials…At a minimum, said the IOM, researchers should discuss LDTs with FDA prior to initiating validation studies, particularly when the test is intended for future clinical use."

Regarding the FDA's case of the Oncotype DX breast cancer recurrence test, the AMP said the test's HER2 biomarker is not intended to be used independently for therapy decisions, including the use of trastuzumab. "FDA seems to presume an intended use that does not exist," AMP wrote in its report.

"There is no distinct [laboratory-developed test]

called 'Oncotype DX HER2 RT-PCR.' The Oncotype DX Breast Cancer Test is a standard of care test that predicts risk of breast cancer recurrence in patients with early stage disease. This information is extremely useful to oncologists in eliminating overtreatment of low risk patients. Although HER2 is among the markers in the test, it is not intended to be independently used for therapy decisions," the AMP report said.

"Although treating physicians requested the individual information for HER2 as a comparator for the commonly used HER2 tests, which occasionally yield ambiguous results, the HER2 information provided as part of the Oncotype DX Recurrence Score must be assessed by physicians in the context of the other clinical and laboratory data in their evaluation of the patient."

The FDA said the HER2 test had poor sensitivity, and that many test samples that were reported as having normal HER2 levels actually had high HER2 levels.

"The underlying issue is that there is no demonstrated direct correlation between number of RNA copies of the gene, the basis for Oncotype Dx HER2 RT-PCR, and the number of protein copies on the cell surface," the FDA's report said. "As a consequence, it is not possible to infer that high or low amounts of RNA correspond to high or low amounts of HER2 protein."

"In 2011, a group of prominent pathologists from three independent laboratories found discrepancies between this HER2 RT-PCR and the FDA-approved tests. The LDT reported large numbers of tumors that tested positive on FISH-HER2 as equivocal (33% of FISH-positive cases) or negative (39% of FISH-positive cases).

"In 2014, the LDT missed all three HER2-positive patients included in a study, diagnosing two as negative and one as equivocal. As a result, the two patients who tested HER2-negative failed to receive trastuzumab, placing them at higher risk for cancer progression."

The FDA report estimated the cost of each false-negative at $775,278.

The AMP's conclusion was that the "Oncotype Dx Breast Cancer Test is used to predict risk of breast cancer recurrence in patients with early stage disease, not to guide decisions about the use of trastuzumab. The test is valid for its intended purpose and FDA review would not have revealed any issues with analytical and clinical validity."

A PDF of AMP's report is available on their website.

Funding Opportunity

AACR and Bayer Offering Research Grants

The American Association for Cancer Research and Bayer announced the 2016 AACR-Bayer Innovation and Discovery Grants program for meritorious projects that examine novel targets and biomarkers in oncology research.

The grants will promote the Bayer Grants4Targets initiative, originally introduced in 2009, to provide new treatment options for cancers with high unmet medical need, encourage innovation and translation of ideas from basic research into novel drugs, and foster collaborations between academic groups and the pharmaceutical industry.

The research proposed for funding should examine novel therapeutic targets focusing on the following oncology research areas: inhibition of cell proliferation; survival signaling; transcription and chromatin modulation; cell cycle regulation; tumor metabolism; hypoxia; immunotherapy; and antibody-drug conjugates.

Each grant will provide $10,000 to $25,000 over a period of one year, with the grant term to begin July 1. All the recipients will be offered the opportunity to work with a Bayer mentor who will provide guidance, expertise, and/or tools to accelerate the translation of their scientific idea.

To complete an application, please visit http://myaacr.aacr.org. Applications must be submitted by Jan. 18. Additional inquiries may be directed to Shaun Fitzpatrick at grants@aacr.org.

In Brief

St. Jude to Open Grad School For Biomedical Sciences

ST. JUDE CHILDREN'S RESEARCH HOSPITAL has received a unanimous vote of approval from the Tennessee Higher Education Commission for the opening of a new graduate school of biomedical sciences.

Stephen White, a faculty member in the St. Jude Department of Structural Biology, will serve as dean of the graduate school. The school will be located in the Marlo Thomas Center for Global Education and Collaboration, and will welcome the inaugural class in fall 2017.

"The graduate school will play an important role in our research efforts to advance cures for pediatric catastrophic diseases," said James Downing, St. Jude president and CEO, "Talented graduate students are a creative and energetic force that will contribute to the kind of innovation required for progress against cancer and other life-threatening diseases. These students will ask the unexpected questions, challenge fundamental assumptions and will help tackle the most difficult scientific problems."

Students will also interact with the neighboring University of Tennessee Health Science Center and Le Bonheur Children's Hospital.

RESEARCH!AMERICA unveiled its policy wish list for 2016, urging Congress to take action on several research priorities.

"Congress should act this year to sustain robust funding for federal health agencies, advance medical innovation and mental health legislation, and permanently repeal the medical device tax," they said in a statement.

The advocacy group said that additional funds for NIH and FDA will support innovative projects including precision medicine, Alzheimer's research and efforts to combat antimicrobial resistance, however "the budget for the Agency for Healthcare Research and Quality was cut by eight percent in the spending bill, further limiting the agency's ability to address costly errors and inefficiencies in health care delivery. Sustainable and predictable investments for AHRQ and other health agencies are critical to accelerating medical progress."

The group also called attention to a bill being drafted by a Senate committee, called the Innovations for Healthier Americans Initiative, which is companion legislation for the 21st Century Cures bill, which passed in the House last year.

"Research!America urges Senate action early this year on legislation that responsibly modernizes regulatory pathways for new drugs and medical devices, and includes mandatory funding for the NIH and FDA. The goal must be to enact meaningful legislation this year."

MEMORIAL SLOAN KETTERING CANCER CENTER opened its **Josie Robertson Surgery Center**. At full capacity, the outpatient center will accommodate 60 surgeries a day.

The facility's 12 operating rooms are designed for procedures for breast cancer and reconstruction, as well as head and neck, gynecologic, and urologic cancers, including procedures that traditionally required inpatient admission. More than 50 percent of the 20,000 surgeries performed at MSK in 2015 were outpatient procedures.

"We are pioneering a new standard for outpatient surgery, one that seeks to transform cancer surgery worldwide," said JRSC Director Brett Simon. "Our commitment to elevating the patient experience is reflected in our emphasis on minimizing the anxiety often felt by patients undergoing cancer surgery. Incorporating technology-based tools—including video conferencing that enables patients to speak with their families or doctors at remote locations and a real-time location system that allows patients to move freely through many parts of the building, both before and after procedures—can help reduce those feelings of anxiety and keep patients focused on the most important thing, their recovery."

The 16-story, 179,000-square-foot building is located on Manhattan's Upper East Side. It was established in part by a gift of $50 million from the Robertson Foundation, which was founded in 1996 by Josephine (Josie) Robertson and her husband, investor Julian Robertson, along with their family. Josie Robertson was elected to MSK's Board of Overseers in 2004.

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INOVA and **George Mason University** formed a partnership to conduct translational research. The partnership was announced by Virginia Gov. Terry McAuliffe.

"By combining resources, Inova and Mason will place Virginia at the forefront of the fight against cancer, heart disease and other life-threatening illnesses," said McAuliffe. "Biomedical research is also a pillar of the 'New Virginia Economy.' The work these two great institutions perform will spur opportunities for entrepreneurship, create new companies and generate jobs that will grow our economy and help us prosper."

The partnership will establish a Scientific Connector Facility and the Inova-Mason Proteomics Center. Both will be housed on the campus of the Inova Center for Personalized Health. Inova will have a physical presence on Mason's Science and Technology Campus so its physicians and researchers can utilize Mason's research capabilities and labs.

Mason and Inova will also establish a Personalized Medicine Public Policy and Ethics Institute, along with an endowed chair to support this initiative. The partnership will also include a fellowship program to recruit internationally recognized researchers and clinical investigators to both institutions.

ST. JUDE announced a $20-million commitment from **The Steven & Alexandra Cohen Foundation** to support inpatient care. The Cohen Foundation's gift will help fund the construction of an inpatient care unit for children treated at the new Kay Research & Care Center on the St. Jude campus.

The third floor of the new Kay Research & Care Center will be home to 17 of the hospital's 51 new inpatient beds, and will be named in honor of the Cohen Foundation. When complete, the new inpatient unit will offer an enhanced patient care experience, with digital technology and more room to accommodate patient and family needs. Patients are expected to occupy the new floors in the Kay Research & Care Center by July 2016.

Drugs and Targets

Breakthrough Therapy Granted To Boehringer NSCLC Inhibitor

FDA granted Breakthrough Therapy Designation to an epidermal growth factor receptor mutant-specific tyrosine kinase inhibitor, BI 1482694 (HM61713).

The designation is based on results from the phase I/II HM-EMSI-101 clinical trial evaluating the treatment of T790M mutation-positive non-small cell lung cancer in patients whose tumors have stopped responding to currently available EGFR-directed therapies. These data were presented at the ESMO Asia 2015 Congress in Singapore and ASCO 2015 in Chicago.

BI 1482694 is an oral, third-generation EGFR mutant-selective TKI developed to specifically target tumors with T790M mutations. The T790M mutation is known as the most common resistance mechanism to develop in response to treatment with EGFR TKIs, according to the drug's sponsor, Boehringer Ingelheim.

In patients with T790M-positive NSCLC who had previously been treated with an EGFR TKI, objective responses (ORs) by independent assessment were observed in 62 percent patients, including 32 (46 percent) patients whose tumor response had been confirmed at the time of data cut-off. Disease control rate was 91 percent by independent assessment. At the time of data cut off, median duration of response had not yet been reached and will be reported at a later date.

The most common treatment-related adverse events included diarrhea, nausea, rash and skin itching.

A global phase II trial, ELUXA 1, has been initiated to evaluate the efficacy and safety of BI 1482694 in patients with T790M mutation-positive NSCLC whose tumors stopped responding to currently available EGFR directed therapies. The primary endpoint of this trial, which is the first in a broad clinical development program for BI 1482694, is objective response rate.

MD Anderson Cancer Center and Kymab announced a partnership in immuno-oncology research.

The program will be conducted with MD Anderson's Oncology Research for Biologics and Immunotherapy Translation unit. The partnership will focus on developing novel human therapeutic antibodies to treat a variety of cancers using Kymab's Kymouse antibody discovery platform. The agreement

is for an initial period of five years.

The ORBIT platform is a centralized organization within MD Anderson, which focuses on translating discoveries into clinically relevant anti-cancer mAbs. ORBIT's scientific directors are Jeffrey Molldrem, professor of the Department of Stem Cell Transplantation and Cellular Therapy, and Michael Curran, professor of the Department of Immunology.

Merck signed a collaboration agreement with Biocartis for the development and commercialization of a new liquid biopsy RAS biomarker test for patients with metastatic colorectal cancer.

The test will be developed on Biocartis' automated molecular diagnostics system Idylla. The new test aims to support clinical practice in performing integrated liquid biopsy RAS biomarker tests, independently of the laboratories' volume of testing or level of expertise.

"Through this collaboration, our desire is to have more metastatic colorectal cancer patients gain access to liquid biopsy RAS testing, regardless of their geographical location," said Rehan Verjee, chief marketing and strategy officer of Merck's biopharma business. "The Biocartis technology will be complementary to other technology previously developed, and will allow for liquid biopsy RAS offerings to a wide range of lab segments, regardless of size and expertise levels."

Guardant Health and Mirati Therapeutics Inc. entered into a collaboration for the development of a circulating tumor DNA assay for Mirati's kinase inhibitor, glesatinib.

Guardant360 is a blood test that identifies multiple tumor mutations across all four types of genomic alterations: single nucleotide variations, copy number amplifications, indels, and fusions. As part of the collaboration with Mirati, Guardant360 will be used to screen NSCLC patients for certain genetic alterations to the MET pathway in order to identify the patients most likely to respond to glesatinib.

The assay will sequence for patients with certain MET mutations and MET gene amplification. This plasma-based assay offers a less invasive approach to assess tumor genetics, avoiding tumor biopsies.

The collaboration will use Guardant360 in Mirati's phase II clinical trial of glesatinib in patients with NSCLC. If successful, the collaboration could result in a regulatory submission and approval of the Guardant360 platform as a companion diagnostic for glesatinib.

"Identifying patients with MET mutations or MET gene amplification is the key to our patient selection strategy. Clinical data has shown that these are the patients most likely to respond to glesatinib," said Charles Baum, president and CEO of Mirati.

"Collaborating with Guardant on a ctDNA assay means that we expect to be able to detect these mutations in a blood sample. This will enable the more than 30 percent of non-small cell lung cancer patients, who have insufficient tumor tissue for biopsy, to be screened for genetic alterations that may be driving their cancer and to seek treatment that could lead to improved outcomes."

Eli Lilly and Co. and Halozyme Therapeutics Inc. entered into a global collaboration and license agreement to develop and commercialize products combining proprietary Lilly compounds with Halozyme's Enhanze platform.

Under the terms of the agreement, Halozyme will receive an initial $25 million payment, followed by milestone payments of up to $160 million for each of up to five collaboration targets valued at up to $800 million. These payments are subject to Lilly's achievement of specified development, regulatory and sales-based milestones. In addition, Lilly will pay Halozyme royalties if products under the collaboration are commercialized.

The Halozyme Enhanze platform is based on a proprietary recombinant human hyaluronidase enzyme (rHuPH20) that temporarily degrades hyaluronan, a chain of natural sugars, to aid in the dispersion and absorption of other injected therapeutic drugs.