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THE CANCER LETTER
Inside information on cancer research and drug development
Vol. 45 No. 36
SEPTEMBER 27, 2019
www.cancerletter.com

JERRY D. BOYD, FOUNDING EDITOR OF THE CANCER LETTER, PIONEER OF CANCER JOURNALISM, DIES AT 91

Nearly half a century ago, Jerry Dock Boyd started covering the opening shots of the War on Cancer.

→ PAGE 5

E-CIGARETTE USE RISES IN YOUNG ADULTS AS COMBUSTIBLE CIGARETTE USE DECLINES

→ PAGE 17

REAL-WORLD EVIDENCE
ONCOLOGISTS QUICKLY REACT TO LABEL CHANGES FOR IMMUNOTHERAPIES, A STUDY BY PENN, FLATIRON SHOWS

→ PAGE 20

IN BRIEF
WINSHIP'S CURRAN RECEIVES ASTRO GOLD MEDAL

→ PAGE 28

TRIALS & TRIBULATIONS
REDUCING RE-EXCISIONS: HOW INTRAOPERATIVE 3-D SPECIMEN TOMOSYNTHESIS ENSURES FEWER REPEAT BREAST CANCER SURGERIES

→ PAGE 32


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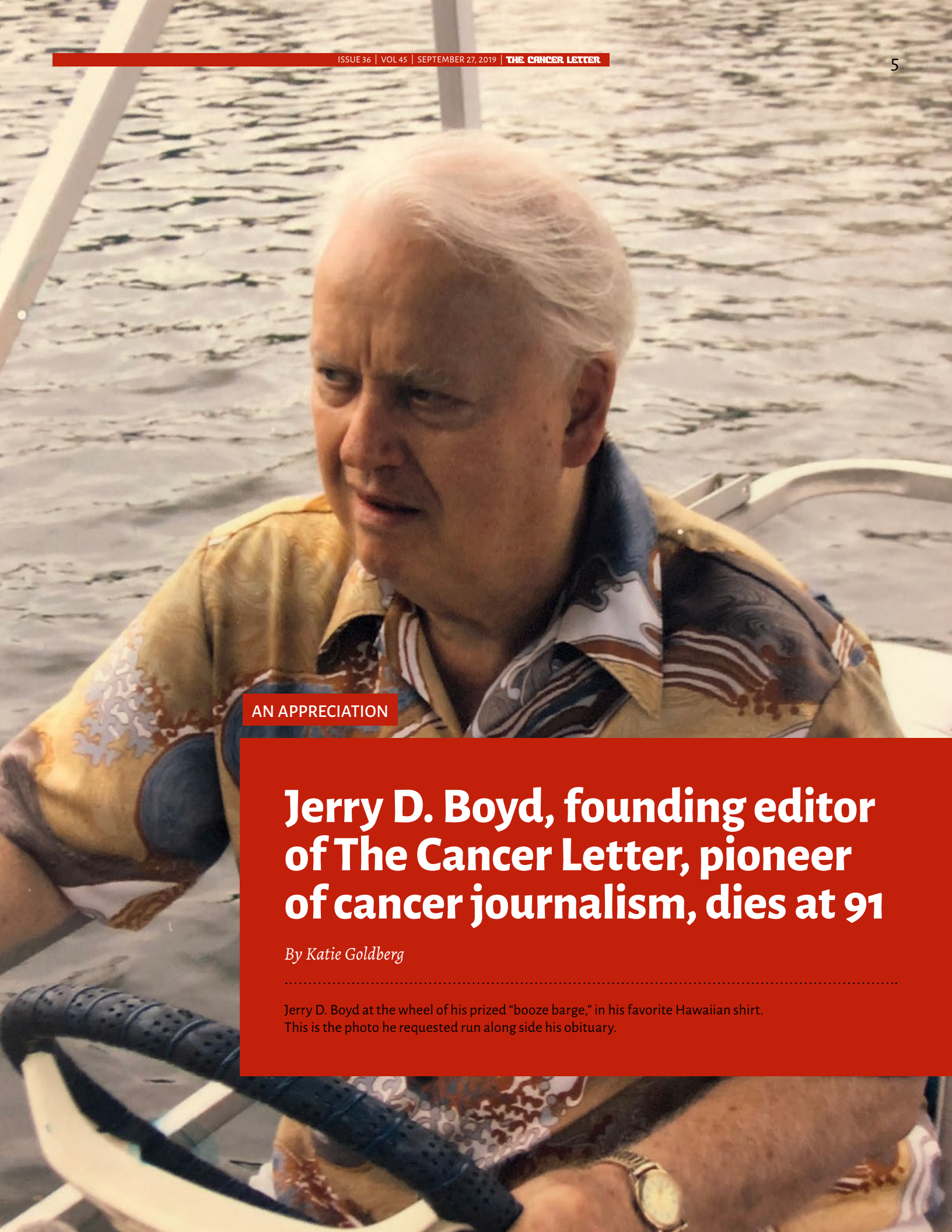
Individual subscriptions $555 per year worldwide. Group subscriptions required for institutional distribution. To subscribe, click here.

ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc.



AN APPRECIATION

Jerry D. Boyd, founding editor of The Cancer Letter, pioneer of cancer journalism, dies at 91

By Katie Goldberg

Jerry D. Boyd at the wheel of his prized "booze barge," in his favorite Hawaiian shirt. This is the photo he requested run along side his obituary.

Nearly half a century ago, Jerry Dock Boyd started covering the opening shots of the War on Cancer.

Richard Nixon was in the White House, ink was drying on the National Cancer Act, money was pouring into the National Cancer Institute, and the cure was said to be around the corner—promises were made that the enemy would be vanquished before the bicentennial.

Boyd, a California sports writer turned Washington reporter, recognized that the community of scientists and administrators that was quickly assembling around cancer research needed a community newspaper.

He created that publication and he called it The Cancer Letter.

"I was struck by the fact that he was always extremely accurate. I don't know if he recorded the board meetings or he took very careful notes, but he never, in my memory, made a mistake," said Vincent DeVita, NCI director from 1980 to 1988. "He always published things just exactly as they happened, so much so that when I retired, I took a microfiche made of all of The Cancer Letter issues. It's like a personal diary of a board meeting."

Boyd died in his sleep Sept. 24, at his home in Reston, VA. He was 91 and had pulmonary fibrosis.

As his granddaughter, and now operations manager of The Cancer Letter, I knew the time would come when this would have to be written. With two generations of journalists on both sides of the family, "who will write the obit" is a dinner-table topic.

Boyd's era in oncology began at a time when giants walked the earth.

Working late one evening, he realized that he needed information about a new chemotherapy drug. To get straight answers, he leafed through the White Pages, found the home phone number of C. Gordon Zubrod, NCI scientific director and a pioneer of platinum chemotherapy. Boyd dialed the number.

"He cut off my apology for calling him at night, at home, and insisted that I should call him any time I have any questions at all about cancer treatment," Boyd recalled later. "Many of my questions were elementary, and I thought perhaps stupid. But Gordon very kindly and without any patronizing explained and answered in ways I could understand."

Boyd regarded people like DeVita and Zubrod as Allied commanders in the War on Cancer. This was a time when group photos of NCI leadership featured white men with box cuts and pocket protectors, and when decisions were being made in smoke-filled rooms.

In his Southern California pastels and conservative in his appearance, Boyd fit in seamlessly. While Boyd himself never smoked, he was a lifelong aficionado of the classic gin martini—Beefeaters, with an olive. He could consume them in increments of four over lunch with Frank J. Rauscher, Jr., NCI director from 1972 to 1976, at O'Donnell's Seafood, across the street from NIH.

Boyd founded The Cancer Letter during the heyday of newsletters. Hundreds of newsletters, covering all industries, were repackaging Washington policy news, providing funding tips, phone numbers of program officers, information from meetings of advisory committees. The Cancer Letter, like most of these publications, was typeset on an IBM Selectric typewriter and pieced together in waxed galleys on a composing table.

Most of these newsletters have gone extinct, and for many years The Cancer Letter has been a newsletter in name only—an homage to our history.

"Prior to the wide-scale availability of the internet and other electronic forms of communication, he provided the gold standard of information flow for scientists and laypeople alike related to cancer research and important funding initiatives and related topics," said Samuel Broder, NCI director from 1989 to 1995. "He was essentially unique in being able to do so. He was brilliant, innately brilliant. So, it was pretty clear that he could pick up complex topics and essentially make them understandable for a wide audience. I think that was a very special skill."

As a sports writer, Boyd knew how to keep the score. As a local journalist, he had a nuanced understanding of how governments function, meticulously tracking the bureaucratic structures and their bureaucrats. Boyd covered cancer like he covered City Hall—and it worked.

"I think he had a very good understanding of it, and how could you not? I mean, he sat through so many of these meetings, it was like going to medical school," DeVita said.

He had swagger, too. As scientists were sorting through miniscule advantages of treatment regimens, he was known to express impatience. "Chuck, don't give this statistical significance crap, just tell me whether it works," he once said to Charles Moertel, the Mayo Clinic expert in colorectal cancer, a proponent of rigorous clinical trials, and a member and chairman of the FDA Oncologic Drugs Advisory Committee.

"He was able to navigate through the topography between the Moertels and the Wolmarks who were barely a whisper at the time. And perhaps we've reverted to that now," said Norman Wolmark, chairman of the National Surgical Adjuvant Breast and Bowel Project.

Sgt. Boyd

Born in San Bernardino, CA in 1928 to Dock Henry Boyd, an electric lineman for the Edison Company, and Loreen Ansley Boyd, a homemaker who worked odd jobs to make ends meet, Boyd was the first member of his family to graduate from high school and the first to graduate from college.

His middle name is the result of a puzzling family story. It began as a family nickname for his grandfather, who, as a child on a farm in Oklahoma was found one day holding a hatchet surrounded by decapitated chickens. He was said to have announced, "I doctored those chickens!" He was henceforth known as "Doc." Then "Doc" became "Dock" to make it look like a real name. His son was named Dock Jr., his grandson Jerry Dock.

A high school student in Ontario, CA, during World War II, he took advantage of a loophole that allowed him to get his driver's license at age 14 and got a job as a school bus driver, driving himself and his classmates to school. He attended Chaffey College, a community college in Cucamonga, for two years before transferring to the University of Southern California, where he received a BA in journalism in 1951.

Boyd worked briefly at the San Bernardino Sun prior to being drafted into the U.S. Army during the Korean War. He didn't mind serving his country, but he wasn't eager to die for it. He performed meticulous research into his options as a draftee, plotting the safest path through the Army. He went so far as to leverage his newspaper connections to get in touch with his Congressman, and interviewed veterans and Marine Corps recruiters.

He had a list, and at the top was the Signal Corps. He bombed the Signal Corps exam, getting tripped up in the Morse code, but he managed to translate his exceptional typing skills into a clerical position. He achieved the rank of sergeant without leaving Ft. Benning, GA.

His war stories are about resourcefulness. While serving as a supply sergeant, he received a letter from a cousin serving in Korea, complaining about the lack of basic supplies, including toilet paper. Boyd, an expert at reading the fine print, discovered that there was no accounting in the Army supply chain for items like toilet paper, so, in a massive overreach, he shipped an entire case to his cousin's unit.

When asked if his time as a supply sergeant helped him with The Cancer Letter, Boyd said, "I probably should have used more that I learned in the Army. That might have been more profitable for The Cancer Letter. I didn't do any market research amounting to anything. The only marketing that I really did for The Cancer Letter is to take the first issue to one of the NCAB meetings."

In 1953, Boyd returned to work at the San Bernardino Sun, where he was a sports reporter and eventually sports editor. He met Jewel (Julie) Purkiss, then a society pages writer and sophomore at UCLA, and proposed on their second or third date—this is a topic of some debate, and an issue of nomenclature. "Another office romance," read the headline on the story about their wedding on the front page of the society section. (Julie still hates that headline.)

Later, the Boyds started a printing business in Highland, CA, and purchased the Highland Messenger, a free weekly community newspaper. He then founded the San Bernardino Free Press in 1964 with local investors—including William Robert "Bob" Holcomb, who later became mayor of San Bernardino—to offer an opposing editorial opinion to the San Bernardino Sun, which had come out in favor of relinquishing San Bernardino's water rights to Los Angeles. Boyd served as the editor.

In 1968, a dispute with Holcomb over journalistic ethics drove him away from journalism. Boyd had seen what he perceived to be a conflict of interest story with deep political reverberations. After Holcomb, who was implicated, refused to run the story, Boyd resigned in protest and brought the story to their competitors. It got ugly.

Boyd, a lifelong Democrat, took a job as an aide for Rep. Jerry Pettis, a Republican, and moved his family, which now included their daughter, Kirsten, to Reston, VA. in 1969.

> "To me, a journalist, the progress in cancer survival and in understanding human biology during the last 20 years has seemed to be the story of the century."
>
> *– Jerry Boyd*

He eventually transitioned back into journalism, landing at the Blue Sheet, a policy newsletter focused on health care then published by F.D.C. Reports, in 1970, shortly before the National Cancer Act of 1971.

It was in his time at the Blue Sheet that Boyd began to see the need for a newsletter like The Cancer Letter.

THE CANCER LETTER | SEPTEMBER 27, 2019 | VOL 45 | ISSUE 36

The story of the century

"To me, a journalist, the progress in cancer survival and in understanding human biology during the last 20 years has seemed to be the story of the century," Boyd wrote in an editorial commemorating the 20th anniversary of the National Cancer Act.

"The ravages of two world wars, the rise of powerful dictatorships and their subsequent demise, space exploration and landing on the moon, were events that dominated the news media in the 20th Century. But as long as mankind exists, the biomedical research progress of the last 20 years should be remembered as the most important news of the era, because millions will continue to owe their lives to it."

At the Blue Sheet, Boyd was increasingly writing about cancer research, watching the magnificence of creation that was unfolding before him. Politics, science, and government were developing structures capable of churning out basic and clinical research on an unprecedented scale. A discipline was emerging, crying out for a chronicler. Boyd saw the biggest story of his life.

"I talked to the publisher and said that I think we ought to devote a section of the Blue Sheet just to NCI and play down some of these other institutes that aren't getting much money. They aren't doing much. Not as much as the cancer people are doing," Boyd said to me when I interviewed him in July. "And he thought about it and he said, 'I don't think we will. I don't think there's enough money in there to support, or potential money in subscriptions, to support that kind of a dedication which would be the space plus at least one salary.'

"I said that I thought that maybe I might try it myself."

Learning from their experience with the Highland Messenger and San Bernardino Free Press, the Boyds founded what became The Cancer Letter.

Boyd (center) with his daughter Kirsten and his wife Julie in 2008.

The entire operation fit into a spare bedroom in their home in Reston. Jerry did the writing, and Julie did everything else. The logo that hearkens to countercultural comic strips was designed by an art student down the street who was paid $60. It has since been updated, but it's basically the same (The Cancer Letter, Jan. 6, 2017).

Over the years, the Boyds tried other ventures—covering AIDS and the National Heart, Lung, and Blood Institute—but these publications never took off. Oncology was a different culture altogether.

"People forget how young the field is," said Robert C. Young, a former NCI clinician-scientist and a former president and CEO of Fox Chase Cancer Center. "In 1960, there wasn't any oncology field. This was a sort of an offshoot of hematology, and most of the medical fields had been in place for a hundred years. But that was not the case with oncology. There was no sort of com-

Paul Goldberg, editor and publisher of The Cancer Letter, and Jerry Boyd drinking martinis at the Boyd Christmas party in 2018.

munication. The field was so young and developed so rapidly that there was this huge expansion. In the early days there were two or three or four cancer centers. Now there are 60 and the whole field has changed. The magnitude of the field has changed."

With a stack of printed up sample issues dated Dec. 21, 1973, and the working name "The Cancer Newsletter," Boyd waltzed into a January 1974 National Cancer Advisory Board meeting, most likely taking what would become his preferred seat in the back row to the left of the conference room door, next to the table where he could quickly grab precious copies of printed materials, and waltzed out with his first check.

The check—for $100—was from John Ultmann, then director of the University of Chicago Cancer Research Center.

The lead story in the first issue of The Cancer Letter gave Ultmann his money's worth: "NCI's Independence To Be Challenged By Edwards When Cancer Act Comes Up For Renewal Next Year."

It's political. It's about money. It's about control. It's about the schism between NCI and NIH leadership—and, in classic Boyd fashion, it includes a quippy pull-quote: "'We wanted to avoid the $1 billion barrier for psychological reasons,' said Sol Spiegelman, NCAB member who headed the subcommittee that made up the recommendations."

The first issue is available here.

"Nobody realized how rapidly the field would grow, how rapidly it would change, and how the information about who was going where and who was doing what and what trials were working early on and so forth—this is the kind of thing that was needed. And there wasn't any mechanism to do that until The Cancer Letter came along," Young said.

As the editor of The Cancer Letter, Boyd made a name for himself as an honest, intelligent, and deeply ethical journalist.

"I was struck by the fact that even as a young investigator, which I was when I first interacted with Jerry, that he would take me seriously," Wolmark said. "He was able to cut through to the crux of the issue with an analytic precision, ask pivotal questions, and really be able to assess the situation with remarkable perspective. There was also an integrity that existed where one would never worry about being misinterpreted or having one's statements distorted. He engendered a sense of trust, which I think was uncommon.

"I certainly ended up liking Jerry a great deal. When Jerry retired, I remember I was walking by the booth at ASCO and saw Paul [Goldberg] and asked him, 'Where is Jerry? I'm not going to talk to you. I don't know who you are, and I don't know whether to trust you or not.'"

Goldberg and Wolmark have overcome this barrier.

THE CANCER NEWSLETTER

11800 Sunrise Valley Drive, Reston, Virginia 22091 Phone 703—471-9695

Volume 1 No. 1

Dec. 21, 1973

Subscription rate: $100 Per Year

NCI's Independence To Be Challenged By Edwards When Cancer Act Comes Up For Renewal Next Year

The Administration will ask Congress to strip the National Cancer Institute of the extra powers it was granted by the National Cancer Act of 1971, unless President Nixon over-rules HEW Secretary Caspar Weinberger and Asst. Secretary for Health Charles Edwards.

The three-year authorization of the act expires next June 30. There is no question it will be renewed, but Edwards has publicly denounced the independence NCI enjoys, particularly in development of its budget. The 1971 act prohibits NIH and HEW from making any changes in the institute's budget request. Only the President, through the Office of Management & Budget, may revise NCI's figures before it goes to Congress.

Edwards insists that the cancer program should be part of his overall "national health strategy," competing for funds on an equal basis with other programs.

The Cancer Newsletter has learned that Edwards, with Weinberger's support, intends to press for a revision that will put NCI back on the same level as other NIH institutes. This would give Edwards veto power over every item in the cancer budget. Edwards has left little doubt that he would exercise that power, on some items at least, if he has the chance.

(continued to back page)

IN BRIEF

Schmidt Sells OMB On Training Grants, But Weinberger Is The One To Convince

Benno Schmidt, chairman of the President's Cancer Panel, feels he made progress when he argued NCI's case on research training grants and fellowships with Office of Management & Budget. In this instance, however, OMB will not have the last word. HEW Secretary Caspar Weinberger decided, when he headed OMB, to kill the NIH training program and wouldn't change his mind after moving to HEW. Congress may have forced Weinberger to back down (See HEW budget story, page 2) . . . . **NCI Director** Frank Rauscher says the most damaging blow to cancer research has been the Administration's ceiling on positions. NCI scientists are doing clerical work because OMB (or Weinberger) won't permit Rauscher to hire more people. Rauscher may put to use the authority he has to bypass HEW and take his case directly to the President, and Congress . . . . **Another level** of contract review may be superimposed over NIH procedures by HEW. Asst. Secretary for Health Charles Edwards is considering establishing review in his office for contracts over $1 million. Rauscher fears this would add 1-2 months to review time already requiring 5-7 months.

The first issue of The Cancer Letter, Dec. 21, 1973.

His middle name notwithstanding, Boyd had no medical or scientific training. He grasped the science he needed to grasp at the time he was covering it. His understanding of large swaths of science was remarkable.

"Most science writers—and I got in trouble once by saying this at a science writers meeting—most science writers get it wrong because science is very complex and very few of them, even the good ones, very rarely get it right when they do it. Jerry was the exception," DeVita said. "He actually got it right, so I always did admire that in him."

> He was able to cut through to the crux of the issue with an analytic precision, ask pivotal questions, and really be able to assess the situation with remarkable perspective.
>
> *– Norman Wolmark*

Knowing that Boyd was there, rapidly taking notes, made DeVita rethink the way he spoke at meetings.

"When I became director of the treatment division in 1974, he covered all the board meetings, and I had a tendency to make quick, attention-getting comments, and he would publish them," DeVita said. "And I'd say, 'Why are you doing that?' because it really annoyed me. I thought about not saying anything at board meetings, because he was right there. But he said to me, 'Well, look, first of all you said it.' And then he said, 'And also, it's accurate. I mean, I reproduced it, and people like those kinds of comments.'

"So, I thought about it, and I said, 'Well, if this turns out to be a good way to get my message across…' So, forevermore, we became symbiotic. I mean, I would make a casual comment that was attention-getting, he would publish it, and I could get a message out, and he was getting something that sold newsletters."

Despite circulation numbers greater than 500 within the first year, Boyd never stopped hand-stuffing the newsletters into the envelopes.

If you received a copy of The Cancer Letter between 1973 and 1989, Boyd had personally taken it to the printing plant, picked it up in a box, and folded it precisely while watching a football game—sometimes one he'd seen before if he liked the outcome.

He took great pride in his product, and would never allow an improperly folded issue, or an envelope with a crooked label, out the door.

This was his Tuesday routine, 46 Tuesdays a year.

Boyd never learned formal shorthand, and instead devised his own. He could transcribe an entire meeting in his shorthand with pinpoint accuracy. Sometimes, on the hunt for a scoop, he'd use his personable nature to evade an embargo by calling every prospective PI for an RFP and deduce who won the contract based on their demeanor. "The guy that wins it, happy as a clam. How do you think all the other contracts that lost the bid on that, how do you think they feel? Unhappy as hell," Boyd said. "One time I did that and, oh damn, it really burned up DeVita, because he hadn't actually made the award yet."

When Boyd retired in 1990, designating his daughter Kirsten as the editor and publisher, he joked that there would be no job at The Cancer Letter for his grandchildren, because cancer would be cured by then.

"We needed cheerleaders," Young said. "We needed people who believed that this could be better. And I think he, even in times when he was critical about something that was going on, he was critical in the sense that he was proposing or advocating for things that would make it better. He recognized that this was something that was going to be big, at a time when a lot of people, including a lot of people in medicine and in science, didn't think so."

In their retirement, the Boyds traveled extensively. Jerry was an avid reader, enjoying every World War II history he could find, and adding to his pile of Washington Post recipe clippings. He also undertook personal projects documenting his family history. His book, "Chester Seth Husted: Letters from a World War I Marine," was self-published in July 2019.

Days before he died, he was contacted by the Corona Historical Society, asking if he would be available for a book signing.

"Jerry's legacy is his uncanny ability to put the data into perspective, to do it with a sense of integrity that engendered trust, and it may perhaps seem simplistic, but I think that's a profound tribute," Wolmark said. "I wish somebody would say that about me when the time comes."

Boyd is survived by his wife of 63 years, Julie Boyd, daughter Kirsten Boyd Goldberg, who served as editor and publisher 1990 to 2010, and granddaughters

Katie Goldberg and Sarah Goldberg, as well as the growing extended family.

> He recognized that this was something that was going to be big, at a time when a lot of people, including a lot of people in medicine and in science, didn't think so.
>
> *– Robert Young*

In July, while he was in home hospice, I sat down with him to document the history of The Cancer Letter. What follows is an excerpt from our three-hour conversation, which spanned everything from the history of oncology to what we were having for dinner.

Katie Goldberg: When did you get the idea for The Cancer Letter?

Jerry Boyd: When I was working for the Blue Sheet, and they passed the National Cancer Act in 1971. I talked to our publisher of the Blue Sheet and Pink Sheet. They weren't making much money on the Blue Sheet, and only part of the time covered the hearings that they had on the bill in Congress. That was the summer of '71 and it was getting close to the time when they finished the hearings.

NIH opposed it. The whole Department of Health, Education, and Welfare opposed it. Only one government agency wanted it and that was the Cancer Institute folks. So, there was some controversy there.

Somebody got word to Ann Landers—I think it was that gal [Mary Lasker], who was a friend of Katharine Graham and had been on one of the breast cancer or other cancer volunteer advisory committees. She got to know some of the people at the Institute, and Ann Landers ordered a call about "horrible cancer," and all the things it does, and how it looks like we're having some breakthroughs come along, all it needs is a few hundred million more dollars to make some progress.

And suddenly, all the trains in the U.S., the freight trains, converged on Washington. All of them filled—and you may think I'm exaggerating but only a little bit—with letters from Ann Landers readers. She was very popular and she urged people to write to Congress, and boy did they ever. I had people up there tell me that they had never seen any response so great.

It passed the House 435 to nothing in favor, and there was only one vote in the Senate against it. That sent all of Congress a message and Richard Nixon the message.

Nixon hoped that it would calm down. His first response was the administration will add $100 million in the current budget to the Cancer Institute's budget that was already submitted, and that was done. But then, later in the year, when they worked on the next year's budget, he didn't put that $100 million in again.

Nixon was determined to try to not have a deficit in the budget, so he resisted putting that back in. Next year, he said, "I thought that was just one year."

Oh no, it's not. We're going to ask for another $100 million next year and so on...

The entire budget was cut way back, so we went down to the deadline where they had to have a continuing resolution. But there were regulations governing how the continuing resolution was to be spread around, and they said the limit could be no higher than the previous year's limit, except if it was already contracted.

For the most part, all the departments had to go by last year's previous resolution. But a lot of the cancer folks said, "Well, you got that extra $100 million and you got it on last year's budget, so you gotta give us that this year." And Nixon said, "No I don't."

I read the rules over very carefully. This was before we started The Cancer Letter. The rules said that if one element, if one major whatever division of the department's budget gets something higher than last year's budget, then everybody has to get it. So I called the Assistant Secretary of Health and asked him, "What about this?"

And he said, "I've never heard of that." And I said, "Well, read the rules." And he said, "Well, let me talk to the Secretary, and he can take it up to Nixon if he thinks they need to do something about it." And about that time, Ted Kennedy filed a lawsuit pointing out somewhat the same thing.

Well, this guy that I talked to in the Assistant Secretary's department called me at the Blue Sheet the next day and said, "You should write your story now. You're going to get the whole $100 million for next year, and it's in there and it'll be the starting point for all the budgets. Not guaranteed there won't be a cut, but that's the starting point."

Was that a scoop for you? Did the Blue Sheet break that story?

JB: Yes. The Blue Sheet broke that story, and it amazed me the power of that little thing, that a little 16-page newsletter can have that impact. Well, the subscription, the number of Blue Sheets was about 1,200. That's a very small amount compared to the multi-billion dollar U.S. budget back in '71, '72.

So, I took some credit for that. Not really much to get any prizes, although if we had taken more credit, we would have. We didn't do that.

When did you realize that you needed to start your own newsletter?

JB: Okay, after that display, and then I was constantly going to cancer meetings, where people would say, "Why don't you put more of this news about the new money coming in and who's going to get it, and we don't know anybody at the Cancer Institute to know who to talk to, and we don't know what's coming up or really what's going on…"

I said sometimes I didn't think that anybody at NCI knew what to do with that money. They said, "You and Blue Sheet ought to do more about it." So, I talked to the publisher and said that I think we ought to devote a section of the Blue Sheet just to NCI and play down some of these other institutes that aren't getting much money. They aren't doing much. Not as much as the cancer people are doing.

And he thought about it and he said, "I don't think we will. I don't think there's enough money in there to support, or potential money in subscriptions, to support that kind of a dedication which would be the space plus at least one salary."

I said that I thought that maybe I might try it myself.

So you wrote it up and got some samples printed?

JB: Of The Cancer Newsletter. And that was the one that was premiered in 1973, with the sample issue.

In December 1973.

JB: In December, yeah. It had 1973 on the date. I took an arm load I guess up to one of the meetings of the NCI in January.

The National Cancer Advisory Board?

JB: Those guys said, "Okay, this is more like it. We got a newsletter with some news about what's going on here."

The very first story was that the Secretary of Health under Nixon was still a little burnt up about being overridden on that $100 million extra money. He told me that he was going to oppose renewing that National Cancer Act of 1971.

It only had one year authorization, and he was going to oppose renewing it, so I put that as the lead story in that sample issue. (The Cancer Letter, Dec. 21, 1973)

Now, I wouldn't swear to it, it was that issue or the real first issue, but it was right in there, and people got excited about that. All this stuff had just gotten started, and they're going to lose their support for it. No way.

Here comes a load of mail again. It wasn't nearly as many as Ann Landers would produce, but we didn't need to bring her out on it again, because just our subscriber list… Well, they weren't subscribers yet, but our mailing list got back and responded enough to it that they convinced the secretary to back off, and Ted Kennedy got into it and started haggling away and the National Cancer Act had no problem getting renewed.

Now, that's when we realized we had enough subscriptions to begin with.

Did you get some subscribers from that first issue?

JB: We got, I don't know how many. The figure two or three hundred comes to mind off that first issue, and then we made an immediate second one, same prospect list. It was the AACR membership list—they gave me their list, even printed the labels for us. That really generated a lot and from those two mailings, we wound up with about five hundred.

Well, that's how much at that time, was $100.

Five hundred subscribers times-

A hundred dollars, that's $50,000 that you got right away?

JB: Yeah.

THE CANCER LETTER | SEPTEMBER 27, 2019 | VOL 45 | ISSUE 36

Wow.

JB: Well, we needed more.

Was that more than you made in a year at the Blue Sheet?

JB: Yeah, that was just in January. But by the start of the new year, after we billed for renewal, we got a very high renewal rate. They started coming in pretty good numbers, too. It wasn't long until we had over a thousand.

What would you say is your favorite story that you've broken in The Cancer Letter?

JB: So, to be an exclusive scoop, it's got to be something that I know that nobody else in the news field knows or will use.

Right.

JB: There were a lot of them, all the time. But real big ones... I guess... Oh, I'll tell you. It might be one of my favorites. I don't know if we would really count this as a scoop, because it's not the kind of story that my only real competitor, the Blue Sheet, would use unless I gave it to him.

It was a story about a division of NCI that was handling the cancer centers grants. They had a meeting of their advisory committee just for their division, and someone on the subcommittee of that advisory committee came up to me while I was there for some other reason and said, "I hope you're not coming to that meeting that my committee is having tomorrow. There's no news. It's just a nothing meeting."

And I said, "You didn't advertise it as a closed meeting."

The government publishes it. And they got to add that in there, notice of the meeting, and what part of it is closed, the topic of what's being discussed and the time. It can only be that part of the meeting can be closed, for only certain reasons.

And so there was this one meeting, she said, "It's just going to be no news, no nothing." And I said, "What are you going to do during that meeting? If it's no news, why did you close it?"

"Well, it's going to be about those requirements we have to get a Cancer Center Support Grant." That's the most important thing that person has to do, and I'd deserve to get knocked out of businesses for not covering that!

And I said, "You just made sure that I was going to be there." C'mon!

It turned out to be about a six month-long hassle, big fight, because it would've kicked three or four sizable cancer centers off the list.

So they wanted it brushed under the rug?

JB: Yeah. That just wouldn't do for me not to be there, not report that.

Right. Especially with your readership.

JB: Yeah. That particular reason is why I'm there.

And to close a meeting and not honestly present what it was that's going to be revealed or discussed... So, I showed up for sure the next day, and they didn't make a thing about it at all. I never had to follow through and fight with them about it.

You don't have to go to court, there's a legal officer in each of the departments who handles it. And I've always been able to get them to back down on that. But I preferred to get to the director, and I was always on good terms with the director.

There were only two of them there that I thought were any good, and a couple that were not very good. And one that was just so-so, but boring as hell.

Do you have any other favorite stories?

JB: Maybe not one but a series of meetings when they were putting together the requirements for the Community Clinical Oncology Program. CCOPs was the acronym.

The idea was that they were having trouble getting enough cancer patients, because the majority were not being treated at the major cancer centers, but by the smaller ones in their own communities.

Right.

JB: The big hassle was always the requirements. Every requirement would freeze out somebody and open the door for others. They are guaranteed to be very rambunctious, argumentative, knock-down, drag-out fights.

They frequently would ask me, "Oh, I said something I shouldn't have. Jerry don't print that." Which is a guarantee that I would print it.

Well yeah, it's part of the public record. That's funny. What about that series of meetings made it your favorite story?

JB: Well, one of them had to do with me making a mistake on one of these programs, a CCOP. It was the one in West Virginia, I believe. I was told by a source that they were going to lose their grant for that CCOP. It was a source that I had used previously quite a bit. They'd never been wrong.

And so, I assumed, which you should never do, that it was correct. So, I used it in the main story on the front page that such and such center is not going to get their grant renewed. And turns out, the NCI had approved it.

Oh no!

JB: I called both as soon as I realized it was wrong. I called people in West Virginia and told them that it's in the mail. I can't stop it, it's too late, it'll be in, so you might want to advise your people out there that see this, or call right now. Tell them that it's coming. Be ready to deny it. And I'm admitting that I made a mistake.

The head of the NCI group that handled that program and approved it, the head of the program that handled all of those particular cancer center grants, I talked to him.

And he said, "I know that the policy at NCI and throughout the government is that we the staff people don't reveal anything until we give the congressman a chance to make the announcement or other people to do something about it or whatever. But in your case, if you call me before you do a story like that again, where there's some information in there that we don't want out until a certain time, and possibly it could be right or wrong, I'll tell you, if you don't reveal the source." And I said "Okay that's a reasonable deal. It's all I ever asked anyway."

So making a mistake got you a really valuable source.

JB: So it did. It got me a valuable source that I may use. And it was always right.

People always assume, oh Vince DeVita, he's a good buddy of Jerry's, they get all this from him. I never got a word from DeVita that he didn't want to get out there, or that he thought he shouldn't get out.

He was good about telling me things that were okay, but on the stuff that was denied to all the news outlets who were interested until a certain date, he was especially determined to keep that quiet. When I broke a story, I made a point of telling him that it did not come from an NCI staff person. I got it from other people.

Any other good ones?

JB: I guess this is good: there was a big contract, came up every five years, in Frederick, Maryland. They took over part of what used to be the biological warfare operation up there. When the government decided to get out of that, they turned over to NIH a major part of that facility. Most of it went to NCI and they put a lot of their programs up there because they ran out of space at NIH.

Every five years, they needed to have a couple of contracts, three or four contracts. The main one, to oversee the basic research that was being done up there. That contract would be pretty sizable, from like $5 million to $10 million a year. That was just one. Each of those other contracts would go to the other companies that were smaller, doing specific types of research, including a lot of them, virology stuff.

They'd put out an RFP, request for proposal, and it would list all of what they had to do.

The laws governing that prohibited NCI employees involved in this from refusing to tell the media the names of the contractors of people that were bidding on these contracts.

Okay.

JB: They had to tell if they were asked. So, it was easy enough to get that list, of course. So, at the start of one of these renewal times, I would call and get that list, getting the name of the principal investigator on each one and his phone number.

> People always assume, oh Vince DeVita, he's a good buddy of Jerry's, they get all this from him. I never got a word from DeVita that he didn't want to get out there, or that he thought he shouldn't get out.
>
> *– Jerry Boyd*

And then I would call each of those guys and just tell them that I'm following this, and I plan to use the news whenever those contracts are awarded.

Award time comes. They are not required to tell the media anything. So, the institute, they're just going to keep things quiet. The individual people don't want the news out unless it's the one guy who wins each contract. The guy that wins it, happy as a clam. How do you think all the other contracts that lost the bid on that, how do you think they feel?

Pretty grumpy.

JB: Unhappy as hell. And we're going to call the guy up and I'd say, "Well how'd you do?" On one hand, I'd hear "That whole thing was rigged. It was rigged." Or "That was set up from the start. They're a bunch of damn liars up there." All this nagging, including all a bunch of four letter words.

Then I'd get one guy and he'd say, "Oh, they did terrific. I can't tell you about it, but we're happy about it."

I would put the names of each one of those, if there were more than one, there usually was. The names of each of the happy guys. He's going to win, he's going to win.

One time I did that and, oh damn, it really burned up DeVita, because he hadn't actually made the award yet.

I said, "Vince, I happen to know from my search that you might want to announce the award yourself that you decided to. So, that's making the award, isn't it?" And he said, "No, it's not making the award until I say it they get it." I don't believe in that.

I have an oversight record on that. I was talking to one of the NCI guys who was always burnt up and went out of his way to really try to keep me from finding out. So I decided to tell him how I did it, just like I told you. I said "It's just being a good reporter."

They gave you all the tools. Process of elimination!

JB: He said, "Ah, that's just rumors. Rumors."

Rumor? Rumor?!

I think that one made me the happiest. And the fact that I could do that with one after another, any contract, where there were multiple applicants, and just one award to be given.

It always worked. But I didn't let them know about it until one guy that I talked to. We got along very well, so I decided, "I'm going to tell you how I get my scoop every year on you guys." And he grumbled "rumors."

You don't know what rumors mean if you think that's a rumor!

I like how simple a solution that is, too. It's very minimal and elegant.

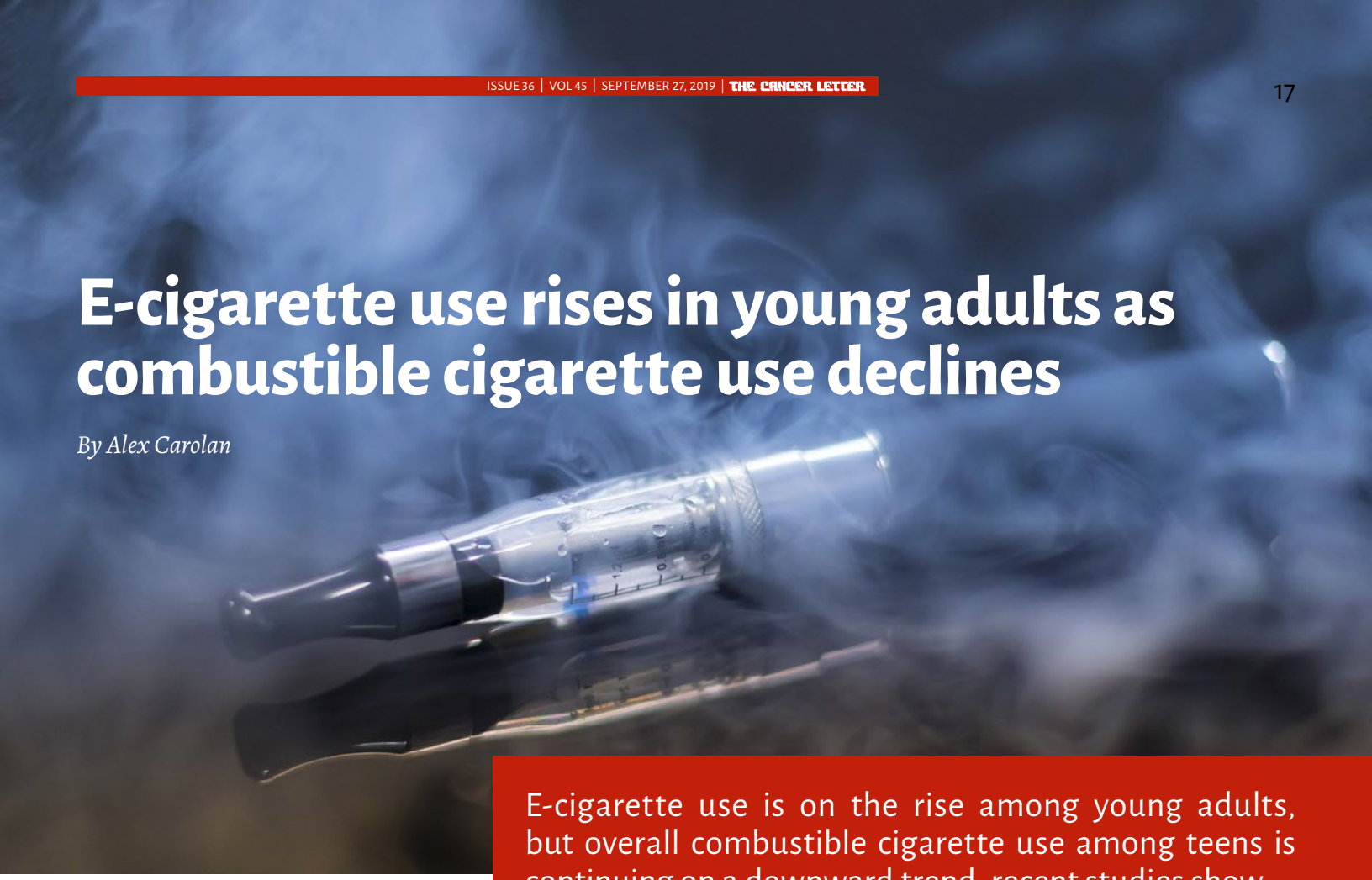
JB: Yeah. I didn't feel delaying something so the congressman could make an announcement was worthwhile.

If you have memories of Jerry Boyd you'd like to share, The Cancer Letter invites you to send them to news@cancerletter.com.

In lieu of flowers, have a martini.

E-cigarette use rises in young adults as combustible cigarette use declines

By Alex Carolan



E-cigarette use is on the rise among young adults, but overall combustible cigarette use among teens is continuing on a downward trend, recent studies show.

One in five young adults regularly uses e-cigarettes and nearly one in four believes e-cigarettes are harmless and not addictive, according to a national cancer survey from the American Society of Clinical Oncology.

ASCO's survey included questions about federal policy on e-cigarettes. In all, 71% of respondents supported FDA regulation of e-cigarettes, 68% supported raising the legal age to purchase e-cigarettes from 18 to 21, 46% supported banning the sale of flavored e-cigarettes, and 41% supported banning all e-cigarettes.

"No e-cigarette products are currently approved by the FDA as cessation aids, and more research to understand these products, the substances in them, and the acute and long-term effects of their use is urgently needed," ASCO Chief Medical Officer Richard L. Schilsky said in a statement.

Overall tobacco product use among young adults has remained stable. But more importantly, the number of youths who vape e-cigarette versus those who smoke conventional cigarettes is changing, said Cliff Douglas, vice president of tobacco control at the American Cancer Society

"[The ASCO survey] underscores what we now understand to be widespread and increasing e-cigarette use by youth and young adults," Douglas said to The Cancer Letter.

Preliminary data from the National Youth Tobacco Survey show that more than a quarter of high school students used an e-cigarette in the past 30 days in 2019. The majority of these were fruit and menthol flavors.

Fewer eighth, 10th and 12th graders are using conventional cigarettes, according to a study from the National Institute on Drug Abuse. In eighth graders, 13% reported using cigarettes in 2015, compared to about 9.1% in 2018. In 10th graders these rates fell from 19.9% to 16%, and in 12th graders these fell from 31.1% to 23.8%, respectively.

"Youth are really not smoking much anymore, and that bodes very well for public health and reduced cancers in America," ACS's Douglas said. Though cigarette use fell from 8.1% to 5.5% overall, vaping rates increased from 21% to 27% in high school students, he said.

"So, [there's] a greater increase in vaping than the drop in smoking, and we don't understand fully the dynamic around that," he said.

High-prevalence of e-cigarette use and nicotine addiction among young adults in addition to a recent outbreak of vaping-related lung illness concerns Doug-

las, and has also led FDA to take action on e-cigarette products such as Juul.

There have been about 805 cases of lung injury reported from 46 states and 1 U.S. territory. Twelve deaths have been confirmed in 10 states. Most of those with the illness reported vaping THC, and many also reported vaping THC in addition to nicotine. Some reported just using nicotine, according to CDC.

FDA sent a warning letter to Juul Labs Inc. Sept. 9 for illegally marketing e-cigarettes, including labelling, advertising, and in one instance giving a presentation at a school. HHS pushed FDA to act, and the agency is expected to enact a policy on flavored e-cigarettes and related vaping products in the coming weeks, Acting FDA Commissioner Ned Sharpless said to reporters Sept. 25.

However, Douglas warned that media scrutiny on vaping could actually increase cigarette use among young adults. A memo from RBC Capital Markets, which Douglas sent to staff at ACS, said the Juul controversy will ultimately not affect Altria, the parent tobacco company behind Juul that has owned 35% of the organization since Dec. 2018.

"The issues with Juul has certainly cast a cloud over Altria's capital allocation, but we remind investors that Juul's current challenges will have no impact on Altria's earnings or cash flow. We also believe the recent media scrutiny on vaping will help overall cigarette consumption. In fact, recent channel checks point to better cigarette volume trends in the first two weeks of September," the memo states.

Essentially, the company believes vaping hysteria in the media will ultimately increase cigarette sales, Douglas said.

"And if that is an unintended consequence of our war on vaping — then that is a real problem for public health. We in the tobacco control community have got to find a sweet spot where we can substantially reduce e-cigarette use in kids."

"We should do everything in our power to prevent a generation of young people from becoming addicted to nicotine, regardless of how it is delivered," ASCO President Howard A. "Skip" Burris III said in a statement.

> "The problem is the industry starting aggressively targeting kids and addicting several million of them to vaping products, exposing young brains to nicotine addiction and potential damage to young brain development."
>
> *– Cliff Douglas*

There isn't enough advertising to counter the tobacco industry's strong public relations campaigns that favor nicotine products, said Alan Blum, director of The University of Alabama Center for the Study of Tobacco and Society and professor and Gerald Leon Wallace Endowed chair in family medicine.

"There's nobody on earth whose job depends on a decline in vaping," Blum said to The Cancer Letter. "There are tens of thousands of new employees at Juul, at Philip Morris [Tobacco], at R.J. Reynolds' [Vapor] Company … whose jobs depend on making sure that some stick with liquid nicotine gets stuck into the mouths of every person they can find."

Juul halted all of its advertising Sept. 25.

Altria owns a 35% stake in Juul. In fact, Juul's CEO Kevin Burns stepped down Sept. 25, and was replaced by Altria's chief growth officer K.C. Crosthwaite. The transition further blurs the line between big tobacco organizations that are often behind e-cigarette companies, Douglas said.

"The positive public health vision for e-cigarettes for those who advocated [for them] is that they'd serve as a much less hazardous alternative to smoking conventional burn tobacco products," Douglas said.

"It remains true that e-cigarettes remain less hazardous. The problem is the industry starting aggressively targeting kids and addicting several million of them to vaping products, exposing young brains to nicotine addiction and potential damage to young brain development," Douglas said.

Flavored e-cigarettes are appealing to young adults, and social media campaigns using influencers to promote vaping products only increase that appeal, Campaign for Tobacco-Free Kids spokesperson Boot Bullwinkle said.

Nearly three in 10 young adults think flavored e-cigarettes are less damaging to a person's health than non-flavored ones. In addition, nearly seven in 10 Americans support raising the legal age to purchase e-cigarettes from 18 to 21, according to the ASCO survey.

"We don't want to see what happened with Juul happen with other nicotine companies … we saw them target kids with their flash social media campaigns," Bullwinkle said to The Cancer Letter. "We want to make sure there's guard rails in place so we don't see the high rates of youth use."

Q & A

Parikh and Adamson spoke with Matthew Ong, a reporter with The Cancer Letter.

THE CANCER LETTER | SEPTEMBER 27, 2019 | VOL 45 | ISSUE 36

REAL-WORLD EVIDENCE

Oncologists quickly react to label changes for immunotherapies, a study by Penn, Flatiron shows

Ravi Parikh
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Staff physician, Corporal Michael J. Crescenz VA Medical Center

Blythe Adamson
Senior quantitative scientist, Flatiron Health

In an unprecedented use of real-world data, researchers at the University of Pennsylvania and Flatiron Health have determined that oncologists are responding quickly to label restrictions announced by FDA.

Researchers found that, in treatment of advanced bladder cancer, there was an adjusted 50% reduction in the use of two immuno-oncology agents within six months after issuance of a safety alert.

The study's findings, published in JAMA Sept. 24, come at a time when oncologists have to keep up with the rapid pace of approval of new therapies. This is especially important in the context of FDA's accelerated approval program, which approves therapies based on metrics that are "reasonably likely to predict" patient benefit.

Using de-identified data from more than 280 oncology clinics across the United States, the study analyzed data on utilization of first-line immunotherapies and chemotherapy in patients with advanced bladder cancer between January 2016 and January 2019. The majority of the patients, 94%, were treated in community practices, with the remaining 6% receiving care at academic medical centers.

The study, Association Between FDA Label Restriction and Immunotherapy and Chemotherapy Use in Bladder Cancer, examined usage rates of PD-1 inhibitor pembrolizumab and PD-L1 inhibitor atezolizumab in advanced bladder cancer patients who are not eligible for standard cisplatin-based chemotherapy.

The two checkpoint inhibitors, manufactured by Merck and Roche, received accelerated approval in 2017 based on phase II studies. However, data from ongoing phase III studies showed patients with PD-L1-negative tumors had decreased survival when taking these drugs, compared to first-line chemotherapy.

This led FDA to issue a safety alert in May 2018, and subsequently restrict the label indications for patients with locally advanced or metastatic urothelial carcinoma. In August 2018, FDA updated the prescribing information for pembrolizumab and atezolizumab to require oncologists to determine PD-L1 levels in tumor tissue of these patients.

"I think in terms of the near 50% reduction in use of immunotherapy, it's encouraging from the perspective that physicians rapidly respond to FDA guidance, which is based on real-time changes in the evidence," Ravi Parikh, lead author of the study, and an instructor in medical ethics and health policy at the University of Pennsylvania, said to The Cancer Letter.

"So, in this case, the FDA warning was based on early reporting of two ongoing clinical trials that looked at the effectiveness of immunotherapy monotherapy as a first-line therapy for bladder cancer versus chemotherapy."

While it wasn't possible to conclusively determine whether all PD-L1-negative patients in the study cohort stopped receiving pembrolizumab and atezolizumab—because not all patients received biomarker testing—the results showed that most oncologists, especially in the community setting, are making clinical decisions that align with evidence-based announcements by FDA.

"The FDA is not mandated to collect information about how providers are using drugs," Blythe Adamson, co-lead author of the study, and senior quantitative scientist at Flatiron Health, said to The Cancer Letter. "Before this study, they really haven't been able to understand whether or not their guidances are being rapidly absorbed, understood, and changing clinical practice to improve patient outcomes."

The study found that rates of PD-L1 testing more than doubled within the same six-month period, from 9.3% to 21.2% per 100 patients.

"That increase in testing is corresponding to the decrease in immunotherapy over time, with the mix of chemo and IO that we're seeing now," Adamson said. "We really hope it's corresponding to the patients who are PD-L1-positive getting the immunotherapy, and the PD-L1-negative patients getting chemo.

"The decrease of 50% [in utilization of first-line immunotherapies for advanced bladder cancer] doesn't mean there's still 50% room to get better. Because the percentage that's left, that doesn't mean that those oncologists are not prescribing the best care. It means that those might be the PD-L1-positive."

Parikh and Adamson spoke with Matthew Ong, a reporter with The Cancer Letter.

Matthew Ong: Is this the first-ever study measuring the compliance of oncologists with FDA label changes?

Ravi Parikh: There have been some studies that look at physician prescribing patterns after randomized controlled trials that are intended to change practice. For example, there was a large trial done with cetuximab in colon cancer, looking at in the impact of randomized trial findings on this prescribing pattern.

But in terms of looking at the effect of an FDA label restriction like this on a drug that received accelerated approval without published evidence being put forth, this is the first study, to my knowledge, that shows that physicians

respond to that warning even in the absence of published evidence.

Blythe Adamson: The FDA is not mandated to collect information about how providers are using drugs. Before this study, they really haven't been able to understand whether or not their guidances are being rapidly absorbed, understood, and changing clinical practice to improve patient outcomes.

Could you briefly describe the specific FDA label restriction that is the focus of your study?

BA: Before the FDA alert, there were many different immunotherapy drugs available to treat bladder cancer: there was pembrolizumab, atezolizumab, nivolumab, avelumab, and durvalumab.

However, when the phase III trial results came out, they showed that patients with PD-L1-negative tumors who received immunotherapy had worse survival than just receiving standard platinum-based chemo. When these phase III trial results became public, an FDA alert was issued at the same time. The updated findings were announced at the big conferences, there were news articles, social media chatter, etc.

So, there was first a big wave of dissemination of information, which led up to the following month, when it became an official label change: patients with PD-L1-negative tumors were not to be treated with immunotherapy. When I first started designing the methods for this study, I used the exact date that the alert was announced; I had expected to see changes to start happening right after the alert. Working closely with Sean Khozin at FDA allowed me to understand the story and timeline from his perspective. And, in his mind, the alert was not the big deal, it was the label change that came a month later.

And so, it was really interesting to listen to his perspective, which was related more to the huge effort and work that it goes into making a label change happen, versus the novelty of the moment that an alert is communicated, and how it's disseminated at medical meetings.

It was very interesting to kind of tie together how this knowledge was spread—from alert to label change. And we picked the date of June 1, right in the middle of when all of these events were happening together.

So, this would also be the first study to look into this matter in real-time, with real-world evidence?

RP: Yes, exactly. In terms of even novel national real-world data sources like Flatiron, or ASCO CancerLinQ, or things like that that have come onto the market over the past two to three years, this is the first study, to my knowledge, that looked at the effect of a label restriction like this, using that data. And I think in some ways it's a really promising avenue for real-world data sources that can look at the effects of these types of FDA policy or label changes in real time.

BA: It's important to have this affirmation and reassurance that the system is working as intended. Because, otherwise, one might think that we should be waiting longer or doing larger studies, collecting more evidence to ensure safety.

In this case, one subgroup of patients with a specific biomarker status wasn't the specific purpose of the earlier trials. It wasn't until additional information came that the FDA was able to reevaluate and provide recommendations on how best to treat these patients.

How did you arrive at the 50% number in this study? I mean, that's a significant "response rate," so to speak, in the reduction of pembrolizumab and atezolizumab in treatment regimens for bladder cancer within six months after FDA restricted the labels for these two immunotherapy agents.

RP: That's a good question. Essentially, on a monthly basis, we looked at the percent of patients that were starting first-line therapy, and then, with that being the denominator, we looked at the percentage that used pembrolizumab or atezolizumab and took that as the numerator.

And then we calculated the adjusted rates, and that's how we arrived at some of the numbers that you see in the paper.

But one of the interesting methodologic techniques that we used is actually extrapolating on prior trends by calculating something called marginal effects, which are the difference between the observed rates minus the predicted counterfactual rates if no label restrictions had been in place.

The average marginal effect is another way of how we arrived at that number.

BA: To estimate the marginal effect of the FDA alert, we used a causal inference method called interrupted time series regression. It takes advantage of time-varying covariates to isolate both the immediate shift in level of utilization and any change in slope, meaning the rate of change in use as increasing or decreasing, attributable to the FDA

alert when controlling for measured confounders.

We found the effect on immunotherapy use was a decrease of 37 percentage points (%-pts), and chemotherapy use had a corresponding increase of 34%-pts because it was the substitution. At the same time, to provide this more personalized care the physicians needed to know PD-L1 status of patients, which is why we observed the doubling of the rate of PD-L1 testing after the alert.

So, is the adjusted 50% reduction rate an encouraging number?

BA: It's absolutely encouraging. It means patients are being purposefully matched to their best hope for treatment given the information known at that point in time. Before the FDA alert and label change, we saw the uptake of immunotherapy shoot up rapidly, as we would expect. There was a lot of hope for these patients.

But, because these drugs were really only able to offer benefit to patients with a specific biomarker status, that means that, after the alert, we would still want to see use of immunotherapy among everyone. Because there's still a population of patients with a biomarker status where it is going to be helpful, and the best drug that they can take.

We wouldn't want to see the immunotherapy rates plummet to zero or continue to rise at the same rate. In both those scenarios, there would be patients who may have achieved better outcomes with a different medicine.

Not only did we see changes in prescribing practices after the alert, but also a doubling of biomarker testing rates. This reflects this new consciousness that a specific group of patients could benefit from immunotherapy.

It is a small step towards capturing the benefits of personalized medicine.

RP: I think in terms of the near 50% reduction in use of immunotherapy, it's encouraging from the perspective that physicians rapidly respond to FDA guidance, which is based on real-time changes in the evidence.

So, in this case, the FDA warning was based on early reporting of two ongoing clinical trials that looked at the effectiveness of immunotherapy monotherapy as a first line therapy for bladder cancer versus chemotherapy.

Right, the phase III trials.

RP: Exactly. Confirmatory phase III trials of the drugs that were approved in the phase II setting and received accelerated approval. And so, I think that the response is encouraging because it's a marked drop in the usage of immunotherapy in a very short time period that is almost entirely explained by the FDA label change.

And so, from the perspective of whether these policies actually work and whether this process works for responding to safety concerns for drugs receiving accelerated approval, it is encouraging in that sense that physicians will actually respond.

Going into the study, were you expecting a higher or lower response rate? And also, what have previous studies shown or not shown?

RP: So, there isn't a huge evidence basis for this, because most of these studies aren't able to study these effects in real time and so, retrospective studies of effect in prescribing patterns are sometimes confounded by the fact that you don't know what's the effect of the label change itself, and what's the effect of , secular trends in practice patterns and introduction of novel therapies.

BA: Ideally, a target trial would be possible if we knew the true biomarker status of every single patient, the treatment they were intended to receive, and the long-term health outcomes.

Then we would be able to tell over time, before June 1, 2018, no matter what your biomarker status was, at one point in time you had like an equal chance of getting immunotherapy or an immuno-oncology agent.

When more information was available and FDA communicated the alert, you would hope that if every single person's biomarker status was known, that they would receive the medicine giving the best chance for the longest survival.

Right, which was why it was important to include looking at rates of PD-L1 testing and see it increase, within six months, from 9.3% to 21.2% per 100 patients.

BA: Yes. In this study, we measured PD-L1 testing rates and prescribing trends across all patients. We did not break down prescribing by PD-L1 test result because the mix of patients who were being tested changed over time. Did everyone with a positive PD-L1 test get the drug that was best for them, with the information known at the time? It's tricky to answer, because there are rea-

sons that some people get tested and some people don't get tested.

So, to me, that increase in testing is corresponding to the decrease in immunotherapy over time, with the mix of chemo and IO that we're seeing now.

We hope it's corresponding to the patients who are PD-L1-positive receiving immunotherapy, and the PD-L1-negative patients getting chemo. This means that we're much closer to all of the patients receiving the drug that gives them the best hope for the longest survival.

It seems a study like this would have been difficult to do, if you had to retrospectively aggregate point of care information without well-curated real-world data.

RP: Exactly. So, from the one study that I cited before, cetuximab in colon cancer, that looked at the effects of prescribing patterns after a large randomized controlled trial, we found nearly similar reduction in terms of magnitude over a multi-year period.

But coming into this study, because that published data wasn't out there, I would have expected personally that, just based on my own practice and based on how much we were using immunotherapy and how much physicians and patients have actually bought into immunotherapy as a first line therapy for cisplatin-ineligible patients with bladder cancer, I would have expected that a label change like this that wasn't accompanied by published data would have not resulted in as large a magnitude in the reduction.

Of course, you would expect a drop in some respects, because it is a change in the label, but not at this magnitude—and also, because the label was only changed for certain patients, patients with PD-L1-negative bladder cancer. So, the fact that we saw reductions in some way across the board for all patients with bladder cancer, was quite remarkable.

Now, I will mention that it's tough to know whether doctors are reducing immunotherapy use for the right patients, the PD-L1-negative patients, because we don't have access to reliable PD-L1 data in this data set. We hope to, but we don't in this data set.

But we can assume that the majority of the reduction is being driven by patients who are likely appropriate, who are patients who are PD-L1 negative. All in all, I think that the results surprised us; even though we were expecting reduction, we weren't expecting it as large as to this magnitude.

So, a pleasant surprise, really.

RP: Yes, absolutely. Now, I think it's one example and it's the first example that has sort of studied a case like this in the accelerated approval process. So, it's encouraging from the respect that this might be a model for responding to FDA safety concerns for drugs receiving accelerated approval.

In some ways, it helps to address some concerns about these processes, about what happens if you introduce drugs that don't necessarily have the gold standard phase III evidence onto the market. So, I think it helps us assuage those concerns in some respects, but there still needs to be data for other types of drugs in this situation.

So, it looks like the Flatiron sample that was used included 280 oncology clinics. Were any academic cancer centers included in the study?

BA: Yes. The study population included 6% of patients receiving care at academic medical centers.

RP: We included both academic and community oncology centers. By virtue of the places that are within the Flatiron Health network, it's predominantly skewed toward community oncology practices. So, that caveat has to be there.

That being said, community oncology is where most people are receiving these drugs and where most oncology care happens, and so we feel that this is a pretty good representation of what's happening out there in the country. My a priori hypothesis is that even if we had sampled academic hospitals or academic campus centers, we wouldn't have seen too many changes in this data.

I see. So, there may not be significant difference in the response between community oncology practices and academic cancer centers?

RP: I don't know if there would be. I mean, the magnitude of response in the community oncology practice is so large that I'm not quite sure if there's much farther for academic practices to go, but it's a question that definitely needs to be answered and probably needs larger follow-up with a data set that involves

a lot more academic centers to help answer that question.

BA: That's a great point, because others have seen differential uptake of novel interventions at academic medical centers compared to community clinics. The 94% community patients in this population represents a random sample of advanced bladder cancer cases in a network of cancer care sites that fit the defined inclusion/exclusion criteria for the study.

The comparison of practice type wasn't a question that we had pre-specified in this case. And I'm not sure, with only 6% of patients in this study receiving care at an academic medical centers, if we would have the sample size with sufficient power to be able to detect a difference.

Sometimes cancer care at academic medical centers is slightly different from community oncology clinics. It's equally important to recognize the mix of patient population can be substantially different too.

Cancer patients at an academic medical center might be sicker, have different cancer types, have more advanced disease stage, or live closer in distance to the clinic. And all of those factors could be related to utilization and outcomes, making it challenging to isolate the impact of differences in practice patterns.

Right, and the biomarker testing rates might be different, and that would influence the proportions of various treatment regimens.

BA: Yes. It can be a pretty tricky comparison.

What are the implications of your study for oncologists everywhere, and what does your study say about importance of uptake and response?

RP: With regard to methodology, I think that emerging real-world data sources serve as a great data source to study real-time changes, and for different prescribing patterns, particularly in response to certain policy changes. And that applies for oncology, but it also would apply for any other real-world data source that has the type of resolution of data that ours had.

With regard to kind of uptake of practice, I think that basically what this shows is that, for drugs that receive accelerated approval that have safety concerns that arise in confirmatory phase III testing, the FDA has a playbook for responding to those concerns in a similar way that it did for atezolizumab and pembrolizumab in bladder cancer; and that it can use emerging data from phase III trials, to inform label changes to drugs and doctors will actually listen to that.

All in all, I think we have some reassurance that evidence-based practice translates relatively quickly in this particular setting.

BA: The implication of this study is that oncologists can continue to be attuned to FDA guidances to offer the best treatment for every patient. The results from this study are encouraging and affirming, given the rapid growth of oncology therapies receiving accelerated approval.

Ideally, if we wait and see when the immunotherapy use levels off to a constant utilization rate, we hope it will correspond to the underlying fraction of the population that is PD-L1 positive. That would mean that patients are receiving the best medicine and hope for good outcomes.

Right, since there isn't sufficient granularity in the data to describe the proportion of these patients that are actually PD-L1-negative, it's hard to define the ideal response rate i.e. for immediate uptake all across the board. That said, since FDA doesn't track clinical decision-making trends, as more data emerge, is there a need for formal accountability on the part of oncologists to keep up with FDA decisions?

RP: Absolutely. With the FDA as the arbiter of emerging safety concerns that come about through clinical trials, I think oncologists are in some ways obligated to observe this data and to respond to it so that we're not exposing patients to potentially unsafe drugs.

As oncologists, we can only base our decisions on the evidence that's available. So, prior to the FDA releasing this warning, we had no indication that there were some of these concerns around immunotherapy monotherapy in first line treatment of bladder cancer, because that data wasn't out there.

So, I think that oncologists certainly have to be vigilant and keep up with these FDA restrictions to ensure the safety of our patients. The onus is also on the FDA and for health systems and other guideline-producing bodies to make that evidence salient to providers, so that we know what we're doing.

> If we hadn't seen these results, it would make one pause and think, 'Do we need to reconsider how we're doing this system?' Or, 'Is it working?' Are our physicians able to stay on top of all the new drugs and all the alerts, so that patients are consistently receiving the best treatments, given the information that's known at that time?
>
> *– Blythe Adamson*

BA: The main takeaway was affirmation of trust in our regulatory system. And I think oncologists are put in a really tough situation with so many new cancer drugs coming out.

I think that it is such a hard, hard thing to stay on top of. If we hadn't seen these results, it would make one pause and think, "Do we need to reconsider how we're doing this system?" Or, "Is it working?" Are our physicians able to stay on top of all the new drugs and all the alerts, so that patients are consistently receiving the best treatments, given the information that's known at that time?

If we do learn that there indeed remains a significant proportion of patients that would not benefit from these drugs, is there anything that can be done to perhaps improve this already excellent response rate? I mean, yes, FDA doesn't regulate the practice of medicine, but are there other ways of improving uptake and response to FDA decisions?

RP: This is an opinion based on the study. A lot of people prior to this study may have argued that you need to publish the full trial before you release this information out to doctors, because who knows whether the safety concerns that arose from the FDA early review of the clinical trials actually pan out? So, there is an argument to be made from some that the FDA may have acted early.

But I think the counterargument, and the one that I believe, is that when these safety concerns arise and when patients are getting exposed to agents that potentially have significant safety concerns or overall survival detriment, that information should be released to physicians even prior to the publication of phase III evidence, because it's our patients' lives on the line.

We really need to have that information in our hands. And what our study shows is that, at least in this case, physicians will respond to it even if given that early information. I think that the blueprint of releasing clinical trial data earlier when safety of patients is an issue, is something that that could and perhaps should be followed.

Perhaps this is an opportunity for health technology companies to develop capabilities—e.g. within Flatiron's OncoCloud—to inform providers and practices about the latest label changes and safety communications from FDA, as well as new evidence from clinical trials, so that timely treatment decisions are being made. I'm certain I'm not the first person to think of this.

BA: I agree that is a promising and useful idea. These types of capabilities are a taste of the early promises of electronic health records—that one day at the point of care what has been learned from many patients will directly inform the next decision.

Demonstrations like this study highlight the progress in cutting down the time from real patient experiences to learning. With recent, curated data, we no longer have to wait years and years and years to collect, process, analyze, report, and then wait for knowledge to spread.

We have a lot of information available to us now, and the technology to process and learn from the data, allowing innovation faster than ever before.

Moving Breast Cancer Treatments Forward

October 30, 2019
Bethesda, MD
8:00am-4:30pm

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Register today for this free conference featuring more than a dozen leading breast cancer researchers. Helen Piwnica-Worms, Ph.D., MD Anderson Cancer Center, will give the 3rd Annual Jayne Koskinas Memorial Lecture and the day's panel topics include:

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- Converging common biology and treatment paradigms in breast and ovarian cancer
- Issues, problems and potentials in breast cancer brain metastasis
- Interdisciplinary collaborations: identifying solutions efficiently

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IN BRIEF

Winship's Curran receives ASTRO Gold Medal

American Society for Radiation Oncology awarded its highest honor, the Gold Medal, to Winship Executive Director Walter J. Curran, Jr., during the 2019 annual ASTRO meeting in Chicago Sept. 14-18.

The Gold Medal is given to ASTRO members who have made outstanding contributions to the field of radiation oncology in research, clinical care, teaching and service.

Curran was recognized for training and mentoring hundreds of oncologists, dedication to patients, and more than 30 years of involvement in and leadership of the national clinical cooperative group Radiation Therapy Oncology Group, now NRG Oncology.

Curran is group chair and principal investigator of NRG Oncology. He is an expert in the treatment of locally advanced lung cancer and malignant brain tumors and was the first radiation oncologist to serve as director of a NCI-designated cancer center. He is a standing member of NCI's Clinical Trials Advisory Committee.

He is responsible for defining a universally adopted staging system for patients with malignant glioma.

Curran also holds the Lawrence W. Davis Chair of Radiation Oncology, chair of Emory's Department of Radiation Oncology and Georgia Research Alliance Eminent Scholar and Chair in Cancer Research.

Fairness to Kids with Cancer Act is introduced in the House

Six members of the House of Representatives recently introduced the Fairness to Kids with Cancer Act (HR-4429), which seeks to adjust federal funding levels for pediatric cancer at a fairer percentage rate than is currently allocated.

Under the act, the percentage of U.S. citizens under the age of 18 would be used to determine the amount of federal funds for pediatric cancer research. This approach is different from the standard approach of apportioning funds based on scientific opportunity.

Reps. Brian Fitzpatrick (R-PA), Josh Gottheimer (D-NJ), Elise Stefanik (R-NY), Mike Kelly (R-PA), Brendan Boyle (D-PA), and Stephanie Murphy (D-FL) introduced the bill.

Brereton, Dornsife receive NCCS Stovall award

Harmar Brereton of Northeast Regional Cancer Institute and Dana Dornsife of Lazarex Cancer Foundation were named recipients of the National Coalition for Cancer Survivorship Ellen L. Stovall Award for Innovation in Patient-Centered Cancer Care.

The award reception will take place Nov. 13.

Brereton served on the staff at Georgetown University for two years and then entered private practice where he spent 33 years developing cancer services by founding the Northeast Regional Cancer Institute in Scranton, Pennsylvania.

At the end of his private practice career, he helped develop The Commonwealth

Medical College, now the Geisinger Commonwealth School of Medicine, where he continues to serve on the faculty as a clinical professor of medicine. In addition to teaching at the Weill Cornell School of Medicine, he is also a leadership team member of the International Cancer Expert Corps.

Dornsife is chair of the board and founder of Lazarex Cancer Foundation, a nationwide public non-profit organization she began in 2006. Lazarex's mission is to improve the outcome of cancer care—giving hope, dignity and life to advanced stage cancer patients and the medically underserved by providing assistance with costs for FDA clinical trial participation, identification of clinical trial options, community outreach and engagement.

Dornsife expanded Lazarex's mission to bring transformational change to the bench to bedside process of clinical trial enrollment, retention, minority participation and equitable access with IMPACT (IMproving Patient Access to Cancer Clinical Trials). Dornsife serves as a board member of the USC Brain and Creativity Institute at University of Southern California, the UCSF Cancer Leadership Council and the Massachusetts General Hospital President's Council.

The Stovall Award is named for longtime CEO of NCCS, Ellen L. Stovall, who died in 2016 due to cardiac complications from her cancer treatments. A cancer survivor of more than four decades, Stovall sought to advance patient-centered care. The Stovall Award is given annually to individuals, organizations, or other entities that have played an important role in improving cancer care.

AdventHealth, Moffitt form collaboration

Moffitt Cancer Center and AdventHealth are partnering to provide cancer treatment and better access to cancer prevention, education, cancer screenings and early phase clinical trials for patients in Florida.

The partnership will develop a cancer research agenda shared across both organizations, which will include expanding research activities and recruitment of innovative cancer investigators to the AdventHealth Orlando and Celebration campuses.

The two organizations plan to establish a clinical research facility and chemotherapy/immunotherapy infusion program at AdventHealth Celebration, focused on solid tumor malignancies and malignant hematology, which will allow Central Florida patients to receive critical treatments closer to home.

At AdventHealth Celebration, researchers from both organizations will conduct early phase clinical studies—the first and only phase I site in Central Florida.

This partnership extends to AdventHealth's West Florida division as well, where a new Moffitt outpatient satellite cancer center is under construction at AdventHealth Wesley Chapel.

UMich and Karmanos get $9.2M prostate cancer SPORE grant

The University of Michigan Rogel Cancer Center and the Barbara Ann Karmanos Cancer Institute received a $9.2 million grant through the NCI's Specialized Program of Research Excellence.

The Michigan Prostate SPORE will focus on critical questions about how prostate cancer develops, with projects designed to address major barriers and challenges in diagnosis, treatment and metastasis.

The Rogel Cancer Center first received a prostate cancer SPORE grant in 1995. It has been continuously funded since then, resulting in landmark discoveries that have identified key genetic drivers of prostate cancer.

In this renewal, the University of Michigan team reached out to Karmanos researchers to leverage the two institutions' strengths. University of Michigan Rogel Cancer and Karmanos are the only two NCI-designated comprehensive cancer centers in Michigan.

"Collectively, we have the opportunity to gain a better understanding of metastatic prostate cancer in many populations and discover additional ways to treat this disease, as well as prevent it," co-PI Elisabeth Heath, the Patricia C. and E. Jan Hartmann endowed chair for Prostate Cancer Research at Karmanos Cancer Institute, and professor of oncology and medicine at Wayne State University School of Medicine, said in a statement.

The Michigan Prostate SPORE is centered on three projects designed to translate laboratory discoveries into clinical advances. Projects range from early detection to tackling castration-resistant metastatic prostate cancer.

1. Understanding a new subset of metastatic prostate cancer. Arul M. Chinnaiyan's lab has previously found 7% of metastatic prostate cancer patients have loss of the gene CDK12. This subset of tumors was produced more immune T cells and laboratory studies suggest they may be responsive to immunotherapy checkpoint inhibitors, a treatment that has overall had limited success in prostate cancer. This project will focus on metastatic castration-resistant prostate cancer with CDK12 mutation, seeking to uncover new treatment targets or biomarkers and to perform clinical trials using immune checkpoint inhibitors.

2. Using a urine test for early detection and high risk. One of the biggest questions in prostate cancer is distinguishing between which tumors are slow-growing, requiring minimal intervention, and which are likely to be aggressive and need immediate treatment. This project will investigate a new urine-based test developed at U-M that looks at a combination of multiple prostate markers, genes and other risk variants. The goal is to improve early detection of prostate cancer in those at high genetic risk and to understand among those diagnosed with prostate cancer who needs aggressive treatment and who may benefit from a less-intensive approach.

3. Overcoming treatment resistance. The hormone androgen plays a key role in prostate cancer, with current treatment including drugs designed to block signals from the androgen receptor. The problem is, nearly all tumors become resistant to these therapies. This project will investigate a new way of targeting the androgen receptor's messenger RNA in the hopes that disrupting the signaling upstream could block any androgen receptor signaling in the tumor, essentially depleting all androgen receptor signaling.

The project is funded through NCI grant P50CA186786-06.

Six researchers receive $14M for cancer genomics research

NIH has awarded six researchers an average total of $2.3 million each to accelerate genomics research over a five-year period.

The researchers received the inaugural Genomic Innovator Awards from the National Human Genome Institute.

Channabasavaiah Gurumurthy, of the University of Nebraska Medical Center; Eric Gamazon, of Vanderbilt University Medical Center; Jason Vassy, of Harvard Medical School; Luca Pinello, of Massachusetts General Hospital; Stacy Gray, of the City of Hope Comprehensive Cancer Center; and Timothy O'Connor, of University of Maryland-Baltimore will serve as principal investigators on the study.

Gurumurthy aims to develop technologies that will address common challenges relating to developing and breeding mouse models. Mouse models are essential for biomedical research, with about 70% of NIH grant applications relating to mouse studies. Given the frequent use of mouse models around the globe, addressing these challenges may have lasting impact on biomedical research.

Gamazon studies the genomic and environmental basis of observable physical characteristics, including hair and eye color, personality traits, and disease risk and resilience. Gamazon will develop computational tools for the analysis of all such observable characteristics relating to medical conditions. Specifically, he will develop methods to advance our understanding of the mechanisms through which genomic variation influences disease risk.

Vassy aims to develop and validate clinical polygenic risk scores for six common diseases: coronary artery disease, atrial fibrillation, type 2 diabetes mellitus, breast cancer, colorectal cancer and prostate cancer. These tests will then be used in clinical trials using point-of-care testing, which provides immediate results to patients where they are being cared for.

Pinello is interested in disease-associated variants that lie in regions of the genome that do not code for genes. Many of these regions regulate expression of genes and are called regulatory elements. Pinello's team will develop approaches to discover and understand how these regulatory elements function and how mutations in these areas can contribute to disease.

Gray has previously shown that people are often unaware that their genome has been sequenced or understand the implications of their results. In addition, many physicians also do not understand the DNA-sequence information gathered. Gray is developing an interactive web-based, point-of-care tool for physicians and patients that will help providers and patients better understand their genomic information. The application will also facilitate the sharing of genomic information within families, ultimately leading to higher quality patient care.

O'Connor focuses on identifying genomic variants that exist in specific ancestry populations. His work aims to classify small segments of identity by descent using genomic variants and to use the data to investigate mutational rates across populations, including how these processes impact human health and disease.

Weitzel and Blazer win ASHG Arno Motulsky-Barton Childs Award

Jeffrey N. Weitzel

Kathleen Blazer

City of Hope's Jeffrey N. Weitzel and Kathleen Blazer are the 2019 recipients of the American Society of Human Genetics' Arno Motulsky-Barton Childs Award for Excellence in Human Genetics Education.

Weitzel is Chief of the Division of Clinical Cancer Genomics and the Cancer Screening and Prevention Program at City of Hope. Blazer directs City of Hope's Cancer Genomics Education Program.

This award recognizes individuals for contributions of exceptional quality and importance to human genetics education internationally. Awardees have had long-standing involvement in genetics education, producing diverse contributions of substantive influence on individuals and/or organizations.

Weitzel and Blazer will receive the award, including a plaque and monetary prize, during ASHG's 69th Annual Meeting Oct. 15 in Houston.

Weitzel and Blazer have worked together for more than 20 years to provide innovative and impactful cancer genomics education to clinicians and researchers from diverse training backgrounds and practice settings across the United States and internationally. Their NCI-funded CGEP initiatives have ranged from educating primary care physicians for referral-level competence, to preparing master's and doctoral clinicians for leadership in translational cancer genomics research.

Jandial receives $1.35M DoD grant for LMD study

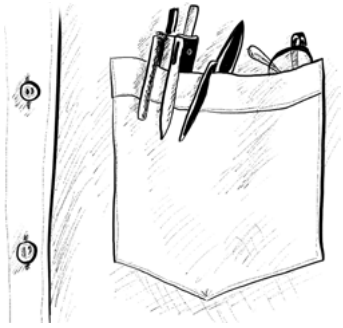
Rahul Jandial has received a $1.35 million grant from the Department of Defense Breast Cancer Research Program to support his laboratory research into leptomeningeal disease.

The DoD's Breast Cancer Research Program awarded the Breakthrough award grant to Jandial, an associate professor in City of Hope's Division of Neurosurgery.

Also known as carcinomatous meningitis, LMD is characterized by the spreading of tumor cells to the lining of the brain and spinal cord. Despite its discovery nearly 150 years ago, it remains the most ominous diagnosis a patient can receive — yet with the fewest treatment options.

THE CANCER LETTER | SEPTEMBER 27, 2019 | VOL 45 | ISSUE 36

THE CLINICAL CANCER LETTER



TRIALS & TRIBULATIONS

Reducing re-excisions

HOW INTRAOPERATIVE 3-D SPECIMEN TOMOSYNTHESIS ENSURES FEWER REPEAT BREAST CANCER SURGERIES

By Roshni Rao
Chief, Breast surgery program,
New York-Presbyterian/Columbia University Medical Center
Associate professor of surgery, Columbia University Medical Center

This year in the United States, nearly 270,000 women will receive the devastating news that they have breast cancer. Many will choose breast-conserving surgery, commonly referred to as lumpectomy, wherein the surgeon seeks to remove the malignant tumor, while also preserving as much healthy breast tissue as possible.

It is a well-established fact that lumpectomy has long been the gold standard of surgical breast cancer care, particularly for women with early-stage disease. It is a far less invasive procedure with a shorter recovery time compared to what patients experience with a mastectomy, in which the entire breast is removed. And according to research, when followed by radiation, lumpectomy yields the same survival rate.

Although lumpectomy is the best option for many breast cancer patients, with 170,000 procedures performed annually, it is not perfect. All too often, a post-operative pathology report shows that while the surgeon may have removed the entire tumor, a second surgical procedure is needed to clean up lingering cancer cells. Known as re-excision, it occurs in roughly 20% to 25% of cases, on average.

When removing a breast tumor, surgeons strive for clean margins. That means targeting not only the tumor, but also excising the surrounding ring of tissue. A pathologist declares the margins clean if no cancer cells are found at the outer edge of that tissue. It is not as simple as it sounds. How much tissue needs

to be removed to ensure a healthy margin has been the subject of considerable debate. Some tumors are difficult to see or feel, which makes them hard to locate during surgery. Localization clips and guidewires inserted into the breast to mark the tumor's location can be difficult to place, and in some cases, can shift position. Still, clean margins are critical to the efficacy of a lumpectomy. Studies show the likelihood of cancer reoccurring is twice as high when doctors fail to achieve adequate margins. Hence, the need for additional surgeries.

But with one in five lumpectomy cases returning to the operating room, the re-excision rate in the U.S. should be lower. It is critical for surgeons and their patients to have access to the latest innovations, once demonstrated effective by clinical research, be used wherever and whenever possible.

Re-excision costs patients, both financially and emotionally. Patients face additional financial burdens, prolonged recovery and heightened anxiety. Scared and frustrated, some women, when faced with a second trip to the operating room, opt for a mastectomy.

As with any surgical procedure, the skill and experience of the surgeon matters greatly, but so does the technology available in the operating room. Re-excision rates can vary wildly from doctor to doctor, and hospital to hospital. So, various medical facilities have highlighted techniques and technologies to reduce second surgeries.

For my practice, intraoperative 3-D specimen tomosynthesis imaging technology has had a profound impact on how surgeries are performed and the results that are achieved.

The technology is already familiar to patients and practitioners as the standard of care in mammography for breast cancer screening. Studies show that 3-D imaging finds more cancer than the traditional 2-D mammograms and reduces the number of false positives. Now, 3-D tomography has radically streamlined breast cancer surgery by allowing surgeons to better visualize the breast and affected area, even through dense breast tissue, in the operating room. With this sort of real-time, actionable information at our fingertips, surgeons can perform more efficiently and deliver better outcomes.

It's like the difference between using an iPhone or relying on dial-up Internet from the 1990s.

Data presented by researchers at the UT Southwestern Medical Center in Dallas during the annual meeting of the American Society of Breast Surgeons in May showed that using 3-D tomography in the operating room reduces re-excision rates by more than 50% compared to the traditional 2-D imaging systems commonly in use.

It also saves time. Surgeons no longer need to wait for tissue samples to be delivered to the radiology and pathology departments for examination, a process that a decade ago routinely took 30 to 40 minutes. So, patients spend less time under anesthesia.

Unfortunately, some hospitals may balk, given the fine line between what's best for the patient and the realities of health care economics. The health care system rewards us for performing more, not fewer surgeries. New technologies are expensive, and this one reduces the need for a surgical procedure that costs between $9,000 and $16,000.

But in the fight against cancer, a single cell can spell the difference between a full recovery or something quite different. Perfection, though impossible, should remain the goal of every breast cancer surgeon. Patients demand the best from their cancer care team, and this includes the most advanced surgical techniques and technologies available.

> “All too often, a post-operative pathology report shows that while the surgeon may have removed the entire tumor, a second surgical procedure is needed to clean up lingering cancer cells. Known as re-excision, it occurs in roughly 20% to 25% of cases, on average.”

CLINICAL ROUNDUP

Breast cancer patients who exercise pre-diagnosis are at lower risk for heart disease

Older patients with breast cancer who exercised before diagnosis may be at a lower risk for cardiovascular disease compared to those who did not, according to a study in JACC: CardioOncology.

Researchers examined 4,015 patients with a confirmed diagnosis of primary breast cancer enrolled in the Women's Health Initiative, which included postmenopausal women age 50-79. Women with cardiovascular disease, a history of any other malignancy prior to enrollment or a body mass index less than or equal to 18.5kg/m2 were excluded.

In the WHI, exercise history at baseline and follow-up were assessed with a questionnaire where patients reported the frequency, duration and intensity of leisure-time physical activity. Researchers examined exercise data that were collected at the visit closest to breast cancer diagnosis and that was between five years and one month prior to diagnosis.

Metabolic equivalent task values were assigned for levels of physical activity per week and exercise was categorized in quartiles: less than 2.5 MET-hours/week (994 patients); 2.50 to greater than 8.625 (1,008 patients); 8.625 to less than 18 (1,011 patients); and greater than or equal to 18 (1,002 patients).

During the study, 324 cardiovascular events occurred. Researchers found that exercising prior to a breast cancer diagnosis was associated with a 20-37% reduction in the risk of first cardiovascular events. The risk of heart attack and heart failure were not impacted, suggesting that exercise may be associated with a greater risk reduction in other cardiovascular events such as angina, coronary revascularization, peripheral artery disease or stroke. Individuals who met current physical activity recommendations (9 MET-hours/week), prior to diagnosis had a 46% lower risk of coronary heart disease death compared to those who exercised less than recommended.

"This study is the first to show the exposure to exercise prior to a cancer diagnosis may potentially protect against or mitigate the established adverse cardiovascular consequences observed in breast cancer patients," lead author Tochi M. Okwuosa, director of the cardio-oncology program at Rush University Medical Center, said in a statement.

One in five young adults regularly uses e-cigarettes and believes they are harmless, not addictive

Roughly one in five young adults uses e-cigarettes daily or recreationally, and nearly one in four believes the products are harmless and not addictive, according to findings from the American Society of Clinical Oncology third annual National Cancer Opinion Survey.

This comes after the Centers for Disease Control and Prevention (CDC) issued the results from its National Youth Tobacco Survey earlier this month, reporting that e-cigarette use among pre-teens and teens is on the rise. It is also despite warnings from the U.S. Surgeon General that e-cigarettes (also known as vapes) contain addictive and harmful or potentially harmful ingredients, including nicotine; lead and other heavy metals; and flavorants such as diacetyl, a chemical linked to serious lung disease.

Amid public debate over banning flavored e-cigarettes, the ASCO survey also found that nearly three in 10 young adults think flavored e-cigarettes are less damaging to a person's health than non-flavored ones. In addition, nearly seven in 10 Americans support raising the legal age to purchase e-cigarettes from 18 to 21.

The National Cancer Opinion Survey is a large, nationally representative survey of the general public conducted online by The Harris Poll on behalf of ASCO.

"We should do everything in our power to prevent a generation of young people from becoming addicted to nicotine, regardless of how it is delivered," said ASCO President Howard A. "Skip" Burris III. "As an organization of cancer doctors, we're also concerned about the potential for e-cigarettes to become a gateway for youth to use cancer-causing tobacco products and the serious side effects that are beginning to emerge."

FDA and CDC began investigating deaths from severe respiratory illness associated with e-cigarette use Aug. 17. Since then, the Trump Administration has announced it plans to ban the sale of most flavored e-cigarettes; at the state level, both New York and Michigan are also enacting bans on flavored vaping products.

The National Cancer Opinion Survey, commissioned by ASCO, was conducted from July 9 - Aug. 10, 2019, among 4,001 U.S. adults ages 18 and over. Of these adults, 195 have or have had cancer. A broader set of survey findings will be released on October 30, 2019.

Troubling Misperceptions about E-Cigarettes Among Young Adults

Among Generation Z (ages 18-22) and Millennials (ages 23-38), the survey found:

- 20% of Generation Z and 24% of Millennials believe e-cigarettes are harmless
- 22% of Generation Z and 24% of Millennials believe you cannot get addicted to e-cigarettes
- 27% of Generation Z and 29% of Millennials think flavored e-cigarettes are less damaging to your health than non-flavored e-cigarettes

Older adults are less likely to hold these misperceptions.

"These beliefs among young adults about e-cigarettes parallel early misperceptions about tobacco products," Burris said. "Education is crucial to correcting misinformation and preventing what could become a public health crisis."

Young People Report Greater Use of E-Cigarettes Than Older Adults

More than one in five Millennials (21%) report being a regular (daily or recreational) user of e-cigarettes, compared to 18% of Generation Z and 15% of Generation X (ages 39-54). In contrast, only 5% of Baby Boomers (ages 55-72) and 1% of the Silent Generation (ages 73 and older) say they use e-cigarettes regularly.

One in six parents (17%) with children ages 9-17 say their children have tried e-cigarettes, with 7% of parents of 9-17-year-olds saying their child uses the products regularly. In addition, 73% of parents with children of those ages say they have talked with their child(ren) about the dangers of e-cigarettes. Children under the age of 18 were not surveyed as part of this research.

Overall, one in eight Americans (13%) report using e-cigarettes regularly. Of them, a majority (80%) currently smoke or have smoked traditional cigarettes in the past.

The majority of this group says they have used e-cigarettes to decrease their use of traditional cigarettes (44%) or to quit smoking them altogether (41%).

"There is no doubt that quitting smoking is one of the best things you can do for your health. If you are trying to quit, we recommend talking to your doctor about methods that are proven to work," said ASCO Chief Medical Officer Richard L. Schilsky, MD, FACP, FSCT, FASCO. "No e-cigarette products are currently approved by the FDA as cessation aids, and more research to understand these products, the substances in them, and the acute and long-term effects of their use is urgently needed."

Americans Support Policy Changes to Address E-Cigarette Use

Amid growing public concern over the dangers of e-cigarettes, even before the recent deaths and investigations linked to e-cigarettes, Americans indicated support for policy change. For example, as of August 10:

1. 71% support FDA regulation of e-cigarettes
2. 68% support raising the legal age for purchasing e-cigarettes from 18 to 21, roughly the same percentage who support raising the legal age for purchasing tobacco products from 18 to 21 (69%)

3. Slightly less than half of Americans (46%) support banning the sale of flavored e-cigarettes, and four in 10 (41%) support banning the sale of all e-cigarettes

"There are so many unanswered questions about e-cigarettes," ASCO Chief Medical Officer Richard L. Schilsky said in a statement. "We need more research about these products so we can begin to answer these questions and protect the health and safety of the American public through education and, where necessary, regulation."

In a 2015 policy statement, ASCO and the American Association for Cancer Research called for a number of steps to be taken in the interest of public health, including requiring e-cigarette packaging to carry safety labels with a warning about nicotine addiction, prohibiting youth-oriented advertising, and banning the sale of e-cigarettes containing candy or youth-oriented flavors unless there is evidence demonstrating these products do not encourage use of e-cigarettes by youth.

Univ. of Arizona researchers look to treat neuropathic pain caused by chemotherapy without using opioids.

A research team at the University of Arizona College of Medicine are developing potent and selective T-type calcium channel antagonists as potential novel pain medicines to treat chemotherapy-induced peripheral neuropathy.

Chemotherapy-induced peripheral neuropathy is detected in 64% of cancer patients during all phases of cancer, but no effective treatment exists, said Rajesh Khanna, professor of pharmacology at the University of Arizona College of Medicine. Khanna is the principal investigator on the study.

The research team's goal is to provide pain relief to cancer patients, increase their compliance of chemotherapy and improve their well-being, he said.

Khanna also is scientific co-founder of Regulonix, LLC., a UA Health Sciences start-up company that received a $341,528 grant from NIH as part of the "Helping to End Addiction Long-Term Initiative" (NIH HEAL Initiative), launched in 2018 to improve prevention and treatment strategies for opioid misuse and addiction and to enhance pain management.

Khanna said the study represents the first step in developing non-opioid pain treatments for chemotherapy-induced peripheral neuropathy. Jun Wang, assistant professor in the department of pharmacology and toxicology in the UA College of Pharmacy and a member of the UA BIO5 Institute, is a key collaborator on this study and created the original compounds that led to development of the compound being tested, called "UAWJ111."

Although initial results in rodent models have been promising, the research is in its very early stages, Khanna cautioned, adding the team also seeks to determine if the new compound has significant side effects and potential for abuse – and whether it also might be effective for other types of pain.

"It's clear that a multi-pronged scientific approach is needed to reduce the risks of opioids, accelerate development of effective non-opioid therapies for pain and provide more flexible and effective options for treating addiction to opioids," said NIH Director Francis S. Collins, who launched the initiative in early 2018. "This unprecedented investment in the NIH HEAL Initiative demonstrates the commitment to reversing this devastating crisis."

DRUGS & TARGETS

FDA approves Janssen's Darzalex for new multiple myeloma indication

FDA approved Darzalex (daratumumab) Sept. 26 in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed adult patients with multiple myeloma who are eligible for autologous stem cell transplant.

The Janssen Pharmaceutical Companies of Johnson & Johnson sponsors Darzalex.

The approval is based on results from the phase III CASSIOPEIA (MMY3006) study that showed the addition of Darzalex to VTd before and after ASCT resulted in deeper responses, as indicated by the higher stringent complete response rate, and improved progression-free survival compared to VTd alone. The approval comes after FDA granted Priority Review for the supplemental Biologics License Application.

"The pivotal phase III CASSIOPEIA study is one of the largest transplant studies ever conducted in multiple myeloma, and the largest study conducted with daratumumab," said Philippe Moreau, principal investigator and head of the hematology department at the University Hospital of Nantes, France. "It's important that patients get a deep response from their frontline therapy, and CASSIOPEIA demonstrates that the addition of daratumumab to VTd before and after transplant markedly increased depth of response compared to VTd alone for patients with newly diagnosed multiple myeloma."

Data from the phase III CASSIOPEIA study were first presented at the 2019 American Society of Clinical Oncology Annual Meeting and simultaneously published in The Lancet. Additionally, updates from the study were recently presented at the 17th International Myeloma Workshop Meeting.

CASSIOPEIA is a two-part, Intergroupe Francophone du Myelome study in collaboration with the Dutch-Belgian Cooperative Trial Group for Hematology Oncology and Janssen Research & Development, LLC. Results from this first part of the trial showed that the primary endpoint of sCR rate post consolidation was significantly higher in the Darzalex-VTd arm compared to VTd alone (29% vs. 20%) (Odds Ratio = 1.60; 95% confidence interval, 1.21–2.12; P=0.0010). The addition of Darzalex to VTd at a median follow-up of 18.8 months resulted in a 53% reduction in the risk of disease progression or death compared to VTd alone (Hazard Ratio [HR] = 0.47; 95% CI, 0.33–0.67; P<0.0001).1

After consolidation, Darzalex-VTd also increased the rate of complete response or better (39% vs. 26%) (OR = 1.82; 95% CI, 1.40-2.36) and very good partial response or better (83% vs. 78%) (OR = 1.41; 95% CI, 1.04-1.92) compared to VTd alone, respectively.

"The Darzalex clinical development program has led to many important firsts, but more importantly, it has generated key insights and understanding into the biology and treatment of multiple myeloma," said Craig Tendler, vice president of clinical development and global medical affairs in oncology at Janssen Research & Development, LLC.

This news comes on the heels of the second approval of Darzalex for treatment of newly diagnosed patients with multiple myeloma who are transplant-ineligible, based on the phase III MAIA study.

Cologuard gets FDA approval for use in younger patients indication

FDA has approved the Exact Sciences Corp. noninvasive colorectal cancer screening test, Cologuard, for eligible average-risk individuals ages 45 and older, expanding on its previous indication for ages 50 and older.

Backed by science and clinical research in collaboration with Mayo Clinic, Cologuard is a stool DNA-based colorectal cancer screening test for average-risk individuals. Cologuard uses a biomarker panel that analyzes a person's stool sample for 10 DNA markers, as well as blood in the stool (hemoglobin).

Last year, the American Cancer Society updated its colorectal cancer screening guidelines to include people between the ages of 45 to 49. The prior ACS recommendation called for screening to begin at age 50 (The Cancer Letter, June 1, 2018).

The label expansion, or broadening of the population for whom Cologuard is FDA-approved, extends screening to approximately 19 million average-risk people in the U.S. ages 45-49.

"About three million people have been screened for colorectal cancer with Cologuard, with nearly half of those surveyed saying they were previously unscreened. With the FDA now approving

the use of Cologuard for this vulnerable 45-49 age group, we are giving health care providers a sensitive, noninvasive option that has the potential to help combat the rise of colorectal cancer rates among this younger group of people," Exact Sciences Chair and CEO Kevin Conroy said in a statement.

Exact Sciences has designed a nationwide user-navigation system that provides 24/7 phone and online support to help people through the process of collecting and returning their samples.

Astellas gets CHMP nod for Xospata as monotherapy for an AML indication

The European Medicines Agency recommended approval for the oral once-daily therapy Xospata (gilteritinib) as a monotherapy for the treatment of adult patients who have relapsed or refractory (resistant to treatment) acute myeloid leukemia with a FLT3 mutation (FLT3mut+).

The Committee for Medicinal Products for Human Use gave the positive opinion. If approved by the European Commission, Xospata has the potential to improve treatment outcomes for AML patients with the most common mutations – FLT3 internal tandem duplication and FLT3 tyrosine kinase domain–and would be one of the few advances for the treatment of AML in Europe over the past 40 years.

Xospata received accelerated assessment from the EMA, which allowed the CHMP to reduce the timeframe for approval. Astellas Pharma Inc. sponsors Xospata.

"The data are encouraging, showing a significant improvement in overall survival, and one-year survival rates doubled when comparing gilteritinib to the current standard of care," study investigator Giovanni Martinelli, Institute of Hematology, S.Orsola-Malpighi University Hospital, Bologna, Italy, said in a statement. "For relapsed or refractory FLT3mut+ AML patients the current prognosis is poor, with median OS of less than six months following treatment with salvage chemotherapy. If approved by the EC, gilteritinib has the potential to change the treatment landscape."

The CHMP decision is based on results from the phase III ADMIRAL trial, which investigated Xospata versus salvage chemotherapy in patients with relapsed or refractory FLT3mut+ AML. Patients treated with gilteritinib had significantly longer OS than those who received salvage chemotherapy. Median OS for patients who received gilteritinib was 9.3 months, compared to 5.6 months for patients who received salvage chemotherapy (Hazard Ratio = 0.64 (95% CI 0.49, 0.83), P=0.0004). Rates of one-year survival were 37% for patients who received Xospata, compared to 17% for patients who received salvage chemotherapy.

In late 2018, Xospata was approved by regulatory agencies in the United States and Japan for the treatment of adult patients who have relapsed or refractory FLT3mut+ AML.

CHMP recommends approval for Bavencio + Axitinib for first-line treatment of advanced RCC

The European Medicines Agency Sept. 20 recommended approval of Bavencio (avelumab) in combination with axitinib for the first-line treatment of adult patients with advanced renal cell carcinoma.

The Committee for Medicinal Products for Human Use gave the positive opinion based on positive findings from the phase III JAVELIN Renal 101 study, which demonstrated a significant extension in median progression-free survival and a clinically meaningful improvement in objective response rate for the combination across all prognostic risk groups compared with sunitinib.

The European Commission will review the opinion, with a decision anticipated in the fourth quarter of this year. Bavencio is sponsored by EMD Serono and Pfizer.

FDA approved Bavencio in combination with axitinib for the first-line treatment of patients with advanced RCC in May 2019. A supplemental application for Bavencio in combination with axitinib in unresectable or metastatic RCC was submitted in Japan in Jan. 2019.

Celsius Therapeutics brings genomics platform to three institutions worldwide

Celsius Therapeutics will apply its proprietary single-cell genomics platform to tissue samples from patients receiving immune checkpoint inhibitor therapies for triple-negative breast cancer, bladder cancer and kidney cancer, at cancer care providers in three countries.

The Parker Institute for Cancer Immunotherapy in San Francisco, Institut Gustave Roussy in Paris, and the University Health Network in Toronto, have access to the single-cell genomics platform. The goal of the collaboration is to discover novel molecular mechanisms and targets for drug discovery.

"The heterogeneity of response in immunotherapy studies suggests that a deeper understanding of disease biol-

ogy and patient subpopulations is needed to fully realize the potential of this approach," Celsius CEO Tariq Kassum said in a statement.

Under these agreements, Celsius will apply its platform approach to generate single-cell data from patient biopsy samples taken pre- and post-treatment with checkpoint inhibitors. In each case, Celsius retains the ability to integrate the clinical information and single-cell genomics data generated from the studies into its growing database. The company plans to use its machine learning algorithms and functional genomics capabilities to rapidly identify and prioritize targets for drug discovery.

Evotec, Takeda collaborate on drug discovery

Evotec SE and Takeda Pharmaceutical Co. Ltd. established at least five joint drug discovery programs.

The goal is for Evotec to deliver clinical candidates for Takeda to pursue into clinical development.

"Collaborating with world-class drug discovery partners like Evotec is central to our model for discovering and developing transformative medicines," Global Head of Research at Takeda Steve Hitchcock said in a statement. "Takeda has a long history of working with Evotec and is confident in Evotec's capabilities."

The collaboration combines Evotec's ability to drive fully integrated drug discovery programs with Takeda's insights into therapeutic approaches in Takeda's four core therapeutic areas: oncology, gastroenterology, neuroscience and rare diseases, in addition to Takeda's insight into development and commercialization.

Evotec will leverage its discovery platform to validate therapeutic hypotheses and advance small molecule programs. Takeda will have options to assume responsibility at lead series when Evotec delivers a preclinical candidate.

Takeda will pay Evotec a one-time, upfront fee to access its platforms. Additionally, Evotec is eligible to receive preclinical, clinical and commercial milestones that can total more than $170 million per program as well as tiered royalties on future sales.

Foundation Medicine, Natera to advance personalized cancer monitoring

Foundation Medicine Inc. and Natera Inc. will collaborate to develop and commercialize personalized circulating tumor DNA monitoring assays, which biopharmaceutical and clinical customers who order FoundationOne CDx would be able to access.

The partnership's focus will be to enable ctDNA monitoring in biopharmaceutical trials in 2020 to establish the clinical utility for these novel assays. Following these studies, a monitoring product will be made available to clinical customers.

"Cancer monitoring is an important part of patient care and developing innovative and more efficient diagnostics for physicians to identify disease progression and therapy resistance earlier is critical," Foundation Medicine CEO Cindy Perettie said in a statement.

The companies will leverage Foundation Medicine's FoundationOne CDx as the baseline test to define a set of unique variants that will subsequently be monitored using a co-developed assay that includes components of Natera's Signatera platform.

The initial focus is to develop personalized cancer monitoring assays that are compatible with FoundationOne CDx as the baseline test, but Foundation Medicine may also elect to expand the scope of the partnership to develop monitoring assays that utilize genomic data generated from Foundation Medicine's FoundationOne Liquid test for solid tumors utilizing ctDNA and/or FoundationOne Heme test for hematologic malignancies and sarcomas.

Foundation Medicine has the exclusive right to commercialize the co-developed monitoring assays. Natera will continue to exclusively offer Signatera testing based on whole exome sequencing of tumor and matched normal DNA.

Foundation Medicine's tests are ordered by physicians for more than 100,000 patients per year, and the company has more than 50 active biopharma partnerships, the company said.

Adaptive Biotechnologies, Amgen use clonoSEQ as preferred MRD test

Adaptive Biotechnologies Corp. entered into a global agreement with Amgen to use Adaptive's next-generation sequencing-based clonoSEQ Assay to assess minimal residual disease across multiple drug development programs within the Amgen hematology portfolio.

Under the four-year agreement, Adaptive will receive annual development fees in addition to sequencing payments and regulatory milestones in exchange for providing MRD testing and analysis for ongoing and future clinical trials.

The partnership, which began in 2016 to assess MRD in acute lymphoblastic leukemia, demonstrates the increasing utility of MRD assessment in the clinic. Adaptive will leverage data generated under this partnership to continue building robust evidence that supports MRD as a validated measure of patient outcomes across multiple novel treatments and blood cancers.