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HOW A NEW JERSEY HOSPITAL USED A MISGUIDED STUDY OF ROBOTIC SURGERY TO WAGE AN ILL-FATED WAR ON BREAST CANCER

Using a da Vinci robot for breast cancer surgery? Is it safe? Effective?

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In this issue

Editor & Publisher
Paul Goldberg

Reporter
Matthew Bin Han Ong

Reporter
Claire Dietz

Designer
Jacqueline Ong

Illustrator & Operations Manager
Katherine Goldberg

Web Developer
David Koh

Editorial, Subscriptions and Customer Service
PO Box 9905 -
Washington, DC 20016

T 202-362-1809
F 202-379-1787
W www.cancerletter.com

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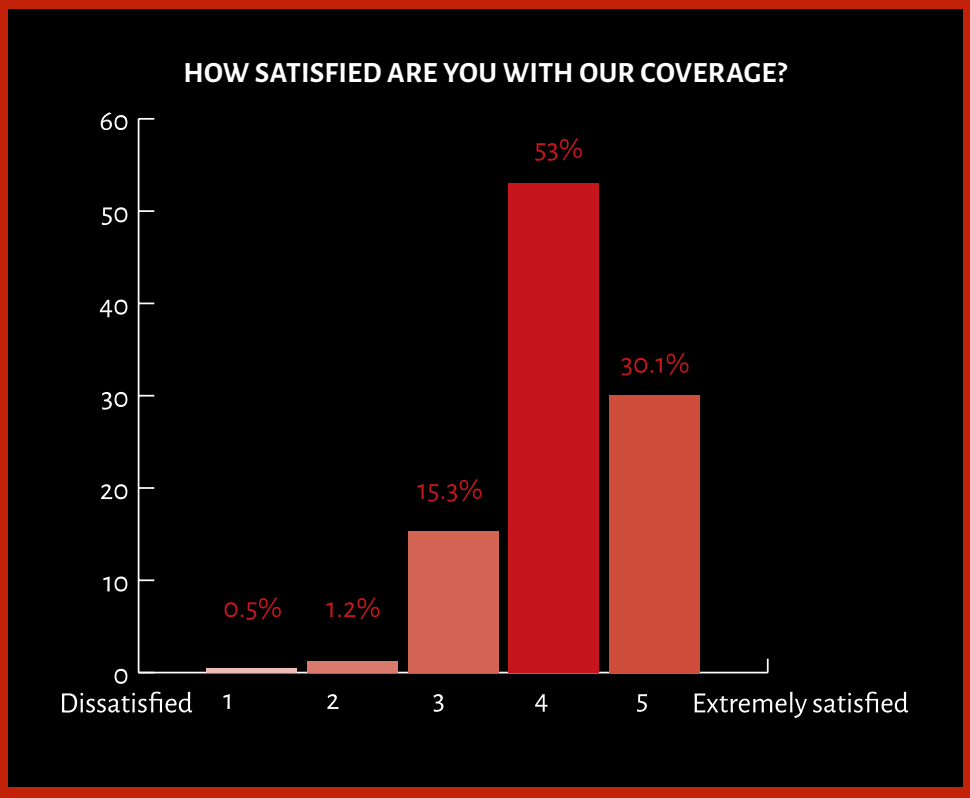
Who are The Cancer Letter readers?

In a survey sent out to The Cancer Letter's weekly mailing list, we asked key questions about our readers, their professional degrees, their fields of interest, and their satisfaction with our coverage.

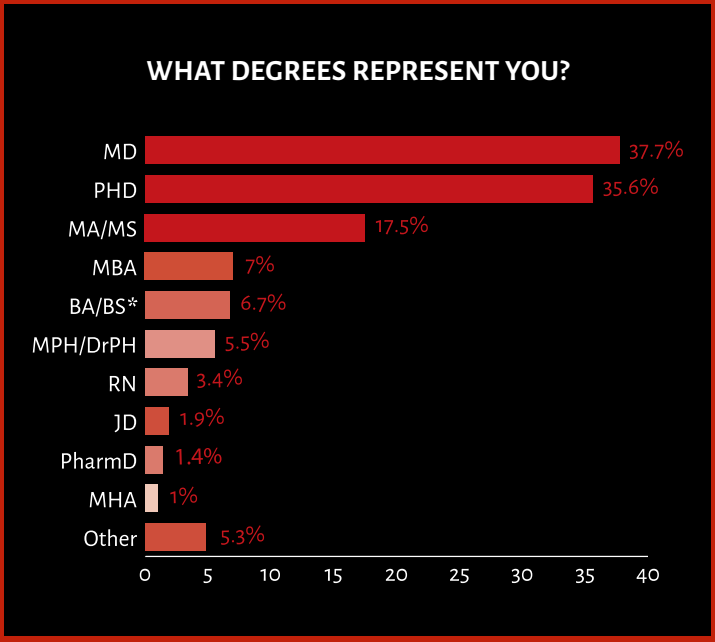
We were pleased to learn that you like us: 83.1% of you rated your satisfaction with our reporting of your areas of interest at a 4 or 5 out of 5, with an average score of 4.1 out of 5 (82%).

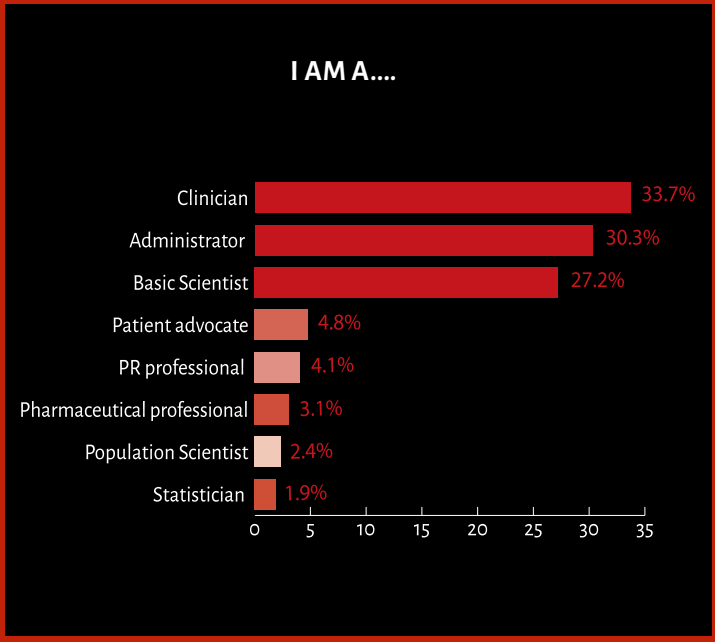
We sent the survey to a list of 6,000 readers, and received 419 responses (7%).



Of the responses, 37.7% are MDs and 35.6% are PhDs. Within that list, 25 are MD PhDs (6%).

You identified yourselves primarily as clinicians (33.7%), basic scientists (27.2%), and administrators (30.3%)—a surprisingly balanced spread.





**terminal degree*

While this survey didn't include the thousands of readers at institutions that distribute the PDF internally, we were pleased to learn that you love reading our PDF edition as well as our online content. Redesigned in 2017, our PDF edition has won design awards, and is a primary way many of our readers access The Cancer Letter.

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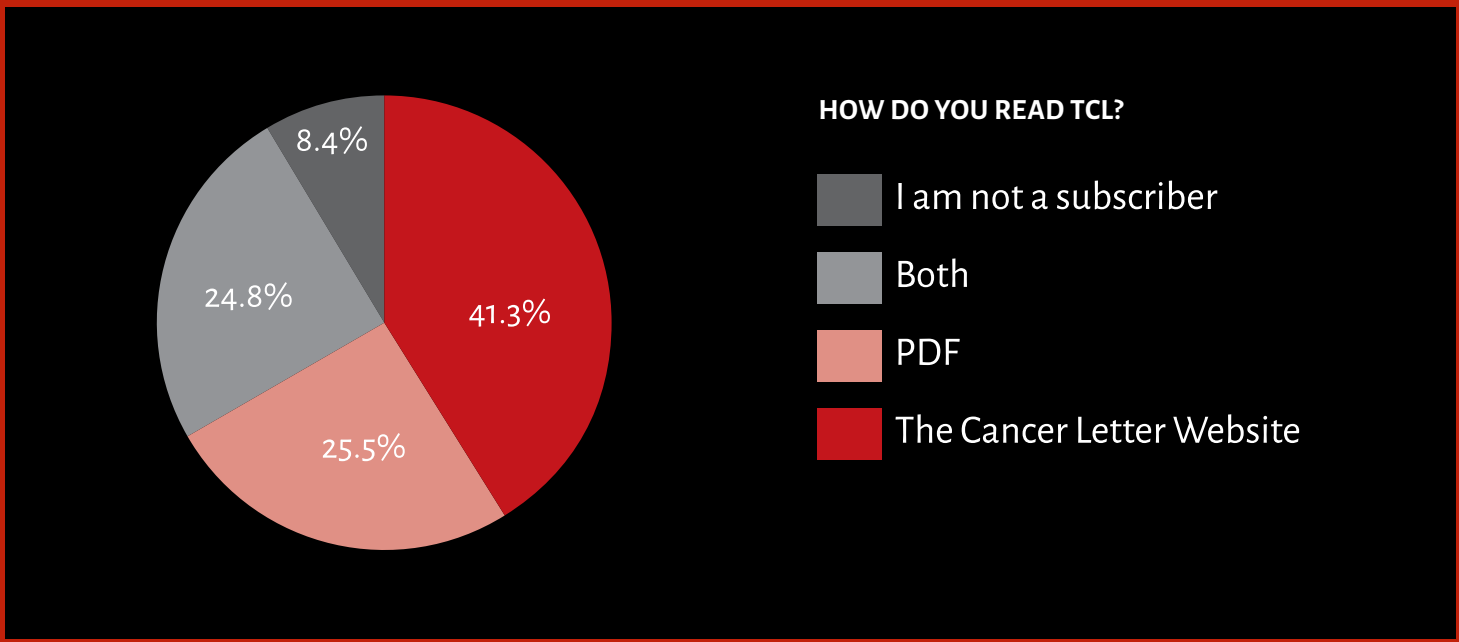

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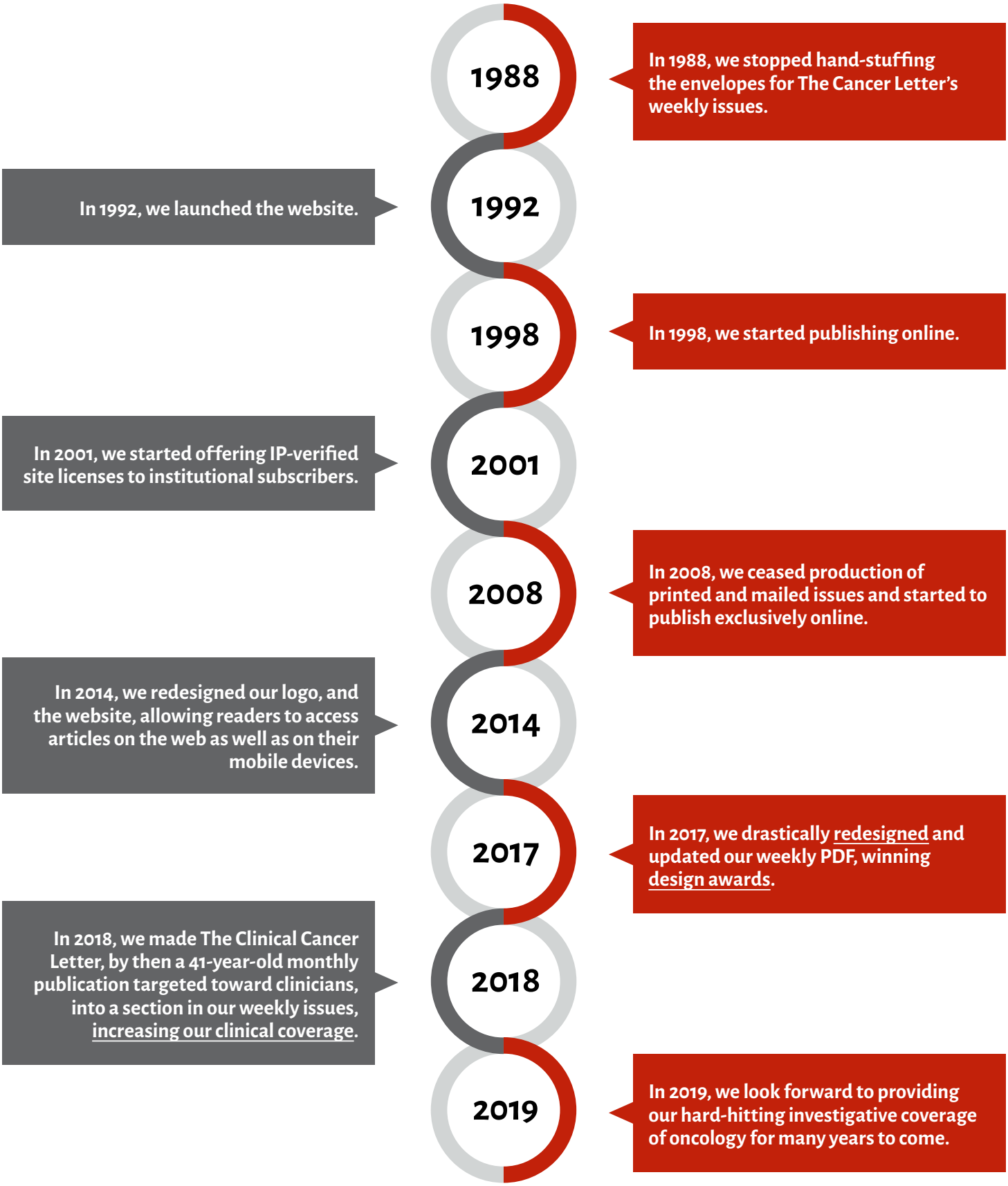

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HOW A NEW JERSEY HOSPITAL USED A MISGUIDED STUDY OF ROBOTIC SURGERY TO WAGE AN ILL-FATED WAR ON BREAST CANCER

By Matthew Bin Han Ong and Paul Goldberg

Using a da Vinci robot for breast cancer surgery? Is it safe? Effective?

You might want to know that, according to informed consent documents for a study that was approved by the IRB at Monmouth Medical Center, all issues stemming from robotic mastectomy have been sorted out:

"You are being asked to participate in this observational study because you are planning to undergo a robotic nipple-sparing mastectomy (RNSM) either for preventative or therapeutic purposes. This procedure has been tested and found successful for the treatment or prevention of breast cancer. You will not be asked to participate in any experimental procedures."

FDA begs to differ. The agency has not cleared the da Vinci Surgical System—the premier device for robotic surgery—for use in treatment or prevention of breast cancer.

Top-tier academic institutions disagree as well. Memorial Sloan Kettering Cancer Center recently reached consensus that the safety of robotic-assisted mastectomy for cancer treatment has not been demonstrated, and researchers at MD Anderson Cancer Center believe that there is enough equipoise around the procedure to justify a large, multicenter randomized trial (The Cancer Letter, April 5).

Folks at the New Jersey hospital apparently felt that, with the pesky issues of safety and efficacy declared resolved, they could justify running an "observational study" focused on patient satisfaction with robotic nipple-sparing mastectomy. The hospital also advised the study's principal investigator, Stephen A. Chagares, a practicing surgeon who has no clinical trials experience, that FDA review was "not applicable."

Well, not quite. In response to questions from The Cancer Letter, FDA said the investigational use of robotic devices in mastectomy procedures would require review by the agency (The Cancer Letter, April 5).

"Wow. I cannot imagine that the hospital thought an Investigational Device Exemption from the FDA wasn't required.

I don't understand that," Rita Redberg, a cardiologist and professor of medicine at the University of California San Francisco, said to The Cancer Letter. "They weren't only throwing the surgeon under the bus, they're throwing their patients under the bus, too."

Monmouth, a hospital with over 500 beds, is a teaching affiliate of the Rutgers Robert Wood Johnson Medical School and a member of the RWJBarnabas Health system. The robotic mastectomy protocol, which received IRB approval on Aug. 15, 2018, was designed to collect patient satisfaction data in the short term as well as outcomes data over 10 years. Up to 50 patients were to be enrolled.

Launching this wow-inspiring effort was the beginning of an ordeal that, according to internal documents and emails obtained by The Cancer Letter, kept getting increasingly weird.

Last October, after two patients—a woman with breast cancer and a man who experienced rapid growth of painful breast tissue—underwent robotic mastectomies at Monmouth, local press declared their treatment a potential "breakthrough."

One reader, Hooman Noorchashm, a surgeon and patient advocate who has been asking tough questions about oncologic safety of several new directions in surgery, wrote a pointed email to Michael Diamond, a reporter who wrote the story for the Asbury Park Press.

It appears that the letter made its way to the executive suite at Monmouth, causing alarm that the hospital might have a problem.

"In November 2018, Dr. Chagares' surgical coordinator tried to schedule an RNSM procedure for a risk-reducing patient. That was the first verbal notification where the hospital informed our group that the procedure was put on hold, without any written confirmation," said Nicholas Fotopoulos, a research coordinator on Chagares's team and an undergraduate student at Princeton University who was involved in the development of the Monmouth protocol.

"[The hospital administration] confirmed via telephone to Dr. Chagares that all RNSMs are completely halted, with no specifics as to why," Fotopoulos said. "I received from that point a phone call from Dr. Chagares, informing me what he had just been told. He said the hospital was concerned by a letter from Dr. Hooman Noorchasm, and I also read the news and the article that was published in the Asbury Park Press."

A conversation with Fotopoulos appears on page 19.

Few if any protocols list emails to reporters at local newspapers among pre-specified reasons for ending a study involving human subjects. Noorchashm confirmed that he had contacted Asbury Park Press.

"I basically told the reporter that he had written an infomercial," Noorchashm said to The Cancer Letter. "I told him that he had not done enough research. I never directly contacted the medical center. He sent my email to the hospital, which was the right thing to do."

Months after enrolling several patients in a surgical outcomes study that isn't designed to assess the safety and efficacy of robotic mastectomy, Monmouth officials publicly announced a moratorium on the procedure in December 2018, citing "safety concerns." (The Cancer Letter, April 5).

Usually, when hospitals stop studies, they inform the investigators and patients. Alas, this didn't happen at Monmouth.

To date, hospital administrators have not provided written justification for the hospital's decision to end the study—leaving surgeons, principal investigators, and patients in the dark as to what the alluded-to "safety concerns" might be.

"This is unacceptable," said Arthur Caplan, the Drs. William F. and Virginia Connolly Mitty Professor of Bioethics at New York University Langone Health and the founding director of the Division of Medical Ethics. "When you're partnering with someone, you don't abruptly end a study without explaining why, without explaining follow-up options, what's going to happen. Are you going to track the people that were in the study, or are you just leaving them in the lurch?"

> "I cannot imagine that the hospital thought an Investigational Device Exemption from the FDA wasn't required. I don't understand that. They weren't only throwing the surgeon under the bus, they're throwing their patients under the bus, too."
>
> *– Rita Redberg*

This was followed by another surprising plot point.

After The Cancer Letter's initial story on robotic mastectomy April 5, Monmouth's chief medical officer, Tom Heleotis, instructed the study's lead PI and surgeon Chagares to stop collecting data.

"All data and study materials related to this protocol must be securely maintained for a minimum of three years; and there should not be any collection of any additional data on the subjects already enrolled," Heleotis wrote to Chagares in an email April 15. Several hospital executives were on the cc: list.

The Cancer Letter sent 64 questions over the past two months to Monmouth, but the hospital has not provided substantive responses to any of these questions, assuring us only that patient safety is their "paramount concern." Our questions and corrigendum to the April 5 story appears here.

"Of paramount concern to Monmouth Medical Center (MMC) is patient safety," the hospital said in a statement April 10 and May 30 to The Cancer Letter. "After an evaluation of the robotic mastectomy procedure, MMC promptly suspended the procedure, pending additional investigation of its risks and benefits."

Chagares declined to speak with The Cancer Letter in detail, citing non-disclosure agreements and attorney's advice.

"Hospital leadership vetted the process the hospital had me follow from the start and re-vetted the process just before the robotic assisted mastectomy I performed when Dr. [Antonio] Toesca [an Italian surgeon who pioneeered the robotic procedure] arrived from Italy," Chagares said in an email to The Cancer Letter May 30.

"Please note that I am at equipoise on robotic mastectomy. I would have been happy to conduct a randomized trial or take part in one. Through this process, I have relied on the directions of the IRB process and guidance from the hospital. I have been explicitly instructed not to communicate with the press throughout this ordeal. I am confident that the hospital and the IRB committee will take this opportunity to answer your important and valid questions."

Surgeon Steven A. Chagares was the PI on an ill-fated study of robotic mastectomy at Monmouth Medical Center.

Fotopoulos, the research coordinator who had worked for Chagares, said the surgeon received no "written official communication as to why a complete moratorium was placed on the procedure."

"We were told to not follow up with those patients; no additional collection of data. That's greatly concerning. It's definitely a threat to patients' health," Fotopoulos said. "Despite these instructions, Dr. Chagares is still following the patients very closely, as he does with all his mastectomy patients, as is the medical standard of care. If Dr. Chagares were to follow through with those instructions, collect no more data, to not observe the health outcomes of your patients—that would be totally inexcusable."

The directive to stop collecting data is even more disturbing, bioethicist Caplan said.

"If you're going to say, 'We're shutting down for safety reasons,' you cannot, must not, leave the subjects or the PI in the lurch," Caplan said to The Cancer Letter. "They see that reported somewhere, they're going to call the PI and say, 'What's going on?'

"Plus, you need to know if there are any adverse events in the study group after the study ends. Who do they report to? Who do they tell? Who is paying? Should something happen, it doesn't mean that, when you shut the study down for

safety issues, there's not going to be a safety issue in a year for somebody."

IDE: "N/A"

Monmouth's handling of the controversy surrounding robotic mastectomy—amidst ongoing debate on cancer-related surgical outcomes—has implications for federal policy on regulation of surgical devices.

How much rigor should be required when surgeons innovate?

In conversations with The Cancer Letter, breast surgeons at MSK and the University of Pennsylvania said they concluded that there are no prospective clinical trial data demonstrating that robotic mastectomy doesn't worsen cancer-related outcomes (The Cancer Letter, April 5).

FDA concurs. In response to the growing use of robotically-assisted surgical devices as well as in response to questions from The Cancer Letter, on Feb. 28, the agency issued an advisory that states:

"The FDA is issuing this safety communication because it is important for health care providers and patients to understand that the safety and effectiveness of using robotically-assisted surgical devices in mastectomy procedures or in the prevention or treatment of cancer has not been established."

In the Feb. 28 advisory, FDA indicated that device manufacturers looking to market surgical tools for use in the prevention or treatment of cancer may now be required to study long-term oncologic endpoints in surgical trials "for time periods much longer than 30 days."

"There is limited, preliminary evidence that the use of robotically-assisted surgical devices for treatment or prevention of cancers that primarily (breast) or exclusively (cervical) affect women may be associated with diminished long-term survival," FDA states in the advisory (The Cancer Letter, March 1).

The agency considers robotic mastectomies to be of "significant risk," which means surgeons and institutions are required to seek an Investigational Device Exemption from the agency to study the procedure on-protocol, FDA officials said.

"While individual health care providers may make individual treatment decisions in the best interests of their patients, any health care provider or health care facility formally studying the safety and effectiveness of the da Vinci for mastectomy would be expected to have an IDE," FDA said to The Cancer Letter.

Hospital administrators advised Chagares's team that an IDE was not necessary, Fotopoulos said.

"The hospital gave us a checklist of everything you need for the protocol to be approved, and one of those items was an IDE," Fotopoulos said to The Cancer Letter. "In the initial consultation meeting, the question of whether an IDE was necessary came up, and we were advised that an IDE was not required. The answer to the question became 'Not Applicable' on the application from there forward."

Fotopoulos's account of events is corroborated by a document labeled "MMC IRB Research Study Review Application," which lists the protocol title as "An Observational Study Evaluating Patients' Satisfaction After Robotic Nipple-Sparing Mastectomy."

The protocol approved by Monmouth's IRB isn't calibrated to demonstrate that the use of a robotically-assisted surgical approach would be "successful" for the treatment or prevention of breast cancer, UCSF's Redberg said.

"A single-arm observational study just at this one hospital? How would they know if this study was successful?" Redberg said. "They're doing a research study for an investigational use on an unapproved indication? So, the IDE should be applicable. I don't know how an IRB could state otherwise."

As it appears, the "observational study" was primarily designed to assess patient satisfaction after robotic mastectomy.

"A trial on robotic surgery would have to have an aim and some way of testing it, other than patient satisfaction. If you look at the protocol title, the robotic surgery is not in the protocol," Rebecca Pentz, professor of hematology and oncology in research ethics at the Emory University School of Medicine, said to The Cancer Letter. "It's all about how the patients felt about it. They're not testing robotic surgery, they're testing patient satisfaction. The endpoint is patient satisfaction."

Generally, it's legal to use a drug or a device in an indication that has not been cleared or approved by FDA, because the agency doesn't regulate the practice of medicine. Also, IRBs have the authority to make independent decisions about whether an "off-label" use poses "significant risk" to patients—although legal experts generally prefer an FDA determination over an IRB's opinion.

Nevertheless, using a drug or device off-label without an IRB-approved protocol, without sponsorship from the product manufacturer, and without an IDE, may expose the practitioner and the provider institution to legal liability.

Internal documents indicate that the Monmouth study is classified as "non-funded research," which means that the hospital did not receive funding from Intuitive Surgical to use its da Vinci robots in mastectomy procedures.

If a surgeon wants to use a device that's already on the market for an indication that hasn't been cleared or approved by FDA—without funding from a de-

vice manufacturer for a formal investigation at the institution—the hospital becomes the sponsor, said Jerry Castellano, corporate director of Institutional Review Boards at the Helen F. Graham Cancer Center and Research Institute, Christiana Care Health System.

"If I decide to get something from a company and I want to use their device in a different way, it puts all the liability on the institution," Castellano, an adjunct associate professor at the University of Delaware, said to The Cancer Letter. "That's a real key factor. The company can say, 'Hey, you did it without following our approval, and therefore you're assuming the liability for doing this.'"

Additionally, Monmouth's statement to patients that robotic mastectomy is "successful" for the treatment or prevention of breast cancer is not only unethical—patients can also sue if their cancer recurs, or if they develop cancer later in life, Castellano said.

"I think this might be a cause for potential litigation," Castellano said. "If the hospital promised that this is going to cure their breast cancer and the patient has a recurrence, it's a bit of a problem.

"That is so unethical, to put something like that in writing and present that to a patient. If they're saying it's been tested, well, show me where. That's really bothersome for a facility to do that."

Christiana would never perform experimental procedures like robotic mastectomy without an IRB-approved protocol that is powered to test long-term safety and efficacy, Castellano said.

"I could tell you, from my perspective all these years, that this would be considered to be completely unethical, and it would not get through our IRB here at Christiana," Castellano said.

Most IRBs will consult with FDA before concurring with a study sponsor that a device is non-significant risk for use in a clinical investigation, if the IRB is uncertain, said a Washington, D.C., attorney who regularly represents device manufacturers and pharmaceutical companies and who has experience with government compliance investigations and enforcement actions.

> If you look at the protocol title, the robotic surgery is not in the protocol. It's all about how the patients felt about it. They're not testing robotic surgery, they're testing patient satisfaction. The endpoint is patient satisfaction.
>
> *– Rebecca Pentz*

"That's often the case," the attorney said to The Cancer Letter. "I imagine there's a range of things that are obvious, but if they're in doubt at all, they're going to want FDA feedback [on whether the device is significant risk or non-significant risk]. So, they will often check with FDA."

A misleading consent form would subject a hospital to liability under common law and tort law, said the attorney, who asked not to be named, because his firm also represents many hospitals and academic medical centers.

"If you assume, hypothetically, that a hospital provided a consent form that is misleading, that would be grounds for potential liability," he said.

Laura Weber, a patient from Illinois who was scheduled to undergo prophylactic robotic mastectomy at Monmouth in January, said the hospital never explained why she could no longer receive the surgery.

"A month before my surgery, Dr. Chagares advised me that the hospital 'halted this operation due to safety concerns,'" Weber wrote in a May 9 email to The Cancer Letter. "The news of this decision was devastating to me. Dr. Chagares and I continued to await notification from the hospital about their concerns, but no information was ever supplied to us.

"As a patient who was given zero voice or any explanation regarding the elimination of robotic mastectomy, I can't help but feel like their goals are more aligned with financial gain rather than patient care," Weber said. "Here, it is May, and I am still waiting for some type of response from the hospital as to why this option was tabled."

In an email response to Weber, Chagares wrote: "As far as the hospital, I have done everything in my power to obtain a letter of clarification defining 'safety concerns' without success ... I stay committed to keeping you informed with any information as I am updated."

Similarly, patients who enrolled in the protocol and underwent robotic mastectomy didn't receive an explanation from the hospital, Fotopoulos said.

"With every change to a clinical trial, typical protocol dictates that you should be given written notification of the change," Fotopoulos said. "To my knowledge, no one has received written notification of that decision by the hospital.

"Looking back now, I experienced Monmouth Medical Center being very enthusiastic about RNSM. They were instrumental in the extensive IRB clinical trial approval process. With all the work that went into development of this clinical trial to obtain their IRB approval, to be very quickly halted, it doesn't make sense."

The hospital's instruction to stop collecting data is troubling, USCF's Redberg said.

"Certainly, medical records are a legal document, and the first thing anyone would ask for in any legal proceeding," Redberg said. "But, by trying to make sure that there isn't any information—because you think it might be damaging to the hospital—conflicts with what should be our main priority, the safety of the patients."

> By trying to make sure that there isn't any information—because you think it might be damaging to the hospital—conflicts with what should be our main priority, the safety of the patients.
>
> *– Rita Redberg*

Monmouth's IRB doesn't have an exemplary track record. In October 2015, the hospital received a warning letter from FDA over "concerns about the adequacy of the IRB's review process."

A review by the agency concluded that Monmouth "did not adhere to FDA regulations governing the protection of human subjects," and found that the hospital's IRB:

- Failed to determine at the time of initial review that studies involving children are in compliance with 21 CFR part 50, subpart D, Additional Safeguards for Children in Clinical Investigations,
- Failed to review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas, and
- Failed to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings.

According to the Code of Federal Regulations and an FDA guidance for IRBs and clinical investigators, "protocol amendments must receive IRB review and approval before they are implemented, unless an immediate change is necessary to eliminate an apparent hazard to the subjects. Those subjects who are presently enrolled and actively participating in the study should be informed of the change if it might relate to the subjects' willingness to continue their participation in the study."

Going forward, such problems at Monmouth would be less likely to occur, at least on the oncology side. As of May 2019, all cancer-related clinical trials in the RWJBarnabas Health system are required to undergo review by the Rutgers Cancer Institute of New Jersey. Cancer-related trials will go through scientific and feasibility review and receive approval prior to IRB review.

Misplaced trust

Chagares is a busy general, laparoscopic, and breast surgeon who has no experience with clinical trials.

Clearly, he got excited by the innovative use of da Vinci robots in breast surgery, and he hired Fotopoulos to handle the paperwork and interactions with the Monmouth IRB.

The surgeon appears to have trusted Monmouth—after all, he was trained there, and has been affiliated with the hospital throughout the 20-plus years that he has been in practice as a surgeon.

This isn't a story about a rogue physician armed with a robot and a surgical personality—as The Cancer Letter's April 5 story on robotic mastectomy may seem to suggest. In fact, Chagares appeared to have followed directives from hospital administrators in a measured way, asking the right questions and applying pressure at the right moments, internal documents and correspondence obtained by The Cancer Letter show.

In the course of reporting the April 5 story, an inside source informed The Cancer Letter that Chagares performed robotic mastectomy on patients without a protocol and without oversight.

This, we later learned, was inaccurate.

Paul Goldberg, editor and publisher of The Cancer Letter, tells how this story grew out of a correction into an investigation. His story appears on page 16.

Documents show that, after reading about robotic nipple-sparing mastectomy in early 2018, Chagares wrote to Antonio Toesca, an Italian surgeon who

pioneered the procedure, to explore training opportunities.

"Dear Dr. Chagares, I am very pleased to know that you are interested in this new surgical procedures," Toesca replied to Chagares in an email April 26, 2018. "The feasibility study on robotic nipple-sparing mastectomy with immediate robotic reconstruction was closed in February 2017 with excellent results. From March 2017, a randomized trial comparing an open surgical arm with a robotic surgery arm is underway. Currently, enrollment is ongoing and I expect to finish the study towards the end of 2018.

"If you want to approach this type of operation, you have three possibilities. The first would be to come and see surgery at the European Institute of Oncology in Milan as an observer in OR."

Enthused, Chagares recruits Fotopoulos as research coordinator, and the two leave for Milan on June 4, 2018.

After observing two robotic mastectomies performed by Toesca, while still in Milan, Chagares wrote in an email to top executives at Monmouth: "The results are great! No scars on the breasts at all. The nipples stay intact. Unbelievable patient satisfaction while still removing all the breast tissue. The results are incredible. The reconstruction is done at the same time via the same 1 inch incision in the axilla.

"As a breast surgeon who has been performing breast surgery for 22 years, I am blown away. Who can I work with who will aggressively assist me in obtaining an IRB in a timely fashion?"

Eric Carney, Monmouth's chief operating officer, hit "reply all" and responded in an email June 8: "The robotic approach seems very innovative. However, we have many questions about FDA, Intuitive and IRB approvals. I agree … to work through IRB and we can model financials."

Chagares, who is certified by Intuitive Surgical to perform robotic surgery, decided that Toesca should be his proctor, at the hospital's invitation.

"Dr. Toesca, from Milan will attend the procedures as my proctor. Please confirm that this is what the Hospital would like me to do," Chagares wrote hospital administrators on June 20, 2018. "Also, can someone advise what process Dr. Toesca needs to follow in order to be the proctor."

Hospital administrators confirmed Dr. Toesca's participation as a proctor for Dr. Chagares on Aug. 6, 2018. Monmouth created a Facebook post on Sept. 14 to announce Toesca's arrival:

"MMC is proud to welcome Dr. Antonio Toesca of the Division of Breast Surgery at the IEO European Institute of Oncology, Milan, Italy," the hospital wrote on its Facebook page. "A noted authority on robotic mastectomy, Dr. Toesca traveled to MMC to observe the hospital's first robotic mastectomy procedure performed by Dr. Stephen Chagares."

As the protocol made its way through the hospital's IRB, top executives offered to engage Monmouth's local marketing firepower.

"I have forwarded to Marketing for awareness and follow up," Monmouth COO Carney wrote in an email Aug. 8. "We would love to support Steven [sic] and assist in awareness campaign for a robotic approach. Very exciting times, thank you for pushing through IRB at MMC."

On Aug. 15, 2018, Chagares received notification that the hospital's IRB committee had voted 8-0 to approve his proposed protocol, titled, "An Observational Study Evaluating Patients' Satisfaction After Robotic Nipple-Sparing Mastectomy (IRB Registration #00003104)."

According to Fotopoulos, Chagares's original draft of the protocol was based on Toesca's Italian clinical trial, which includes cancer patients and high-risk patients who were candidates for traditional skin, nipple and areola-sparing mastectomy.

"We were also monitoring oncologic outcomes to make sure that, with regular follow up with Dr. Chagares, these patients were staying healthy, they were pleased with their cosmetic outcome, the cancer wasn't returning and the oncologic outcomes were the same or better than standard surgery," Fotopoulos said.

In the correspondence, there are no indications that Chagares and his team are aware of the fatal flaws that the IRB was introducing into his protocol.

"The IRB committee itself worked with us pretty much in every step of the way in order to design the protocol. We wanted to make sure we did everything correctly," Fotopoulos said. "The IRB committee had their own input on revisions multiple times throughout the admission process. We made every modification they requested. Monmouth Medical Center made a multitude of direct edits to the protocol, consent, and other accompanying documents until they deemed them satisfactory. Monmouth Medical Center, and the IRB committee, specifically, was with us every step to make sure that this protocol was as it should be."

The end result was a protocol that was edited, vetted, and unanimously approved by members of Monmouth's IRB, Fotopoulos said.

Mistakes were made. The person or persons who edited out the control arm from Toesca's study apparently neglected to change one of the protocol's primary hypotheses: that the use of a robotic device to perform a nipple-sparing mastectomy does not worsen the oncologic outcome of patients with breast cancer or BRCA mutation.

After being dismantled and reconstituted, the Monmouth protocol sim-

ply doesn't provide the data for a hypothesis test.

Why would Monmouth offer robotic surgery for an unapproved indication to patients without a safety and efficacy protocol, promise high-risk patients that the procedure is "successful" for use in said indication, and simultaneously enroll patients in a data collection protocol to assess whether the procedure worsens oncologic outcomes?

"This is concerning on so many levels, and it contradicts itself," Otis Brawley, Bloomberg Distinguished Professor of Oncology and Epidemiology and associate director for community outreach and engagement at the Bloomberg School of Public Health and Johns Hopkins Kimmel Cancer Center, said to The Cancer Letter.

Patients shouldn't participate in research that's not going to answer a scientifically valid question, Emory's Pentz said.

"If you have a study which is hypothesis-driven, and if you have to close the study when your sample size is too small to get any good data—and if the follow-up data will not provide useful scientific information—then you should not continue to collect protocol data," Pentz said. "The courteous thing to do would be to say, thank you participating in our trial, unfortunately we've had to stop, we won't be calling you in the future, we still appreciate your help."

"IRB ACTION: Closed"

Internal documents and correspondence show that least six top executives at Monmouth had in-depth knowledge about the adoption of robotic mastectomy procedures at the hospital, as well as the evolution of Chagares's protocol, from conception to termination:

- Bill Arnold, president and CEO
- Eric Carney, chief operating officer
- Tom Heleotis, chief medical officer
- Joseph Jaeger, associate vice president of academic affairs and acting chair of the Institutional Research Review Board
- Barbara Mihelic, director of clinical research - IRB
- Manpreet Kohli, director of breast surgery

"When you first reached out, Dr. Chagares referred to the hospital administration, and they said there were very strict media guidelines for IRB clinical trials and he was told not to speak with The Cancer Letter," Fotopoulos said. "I believe you reached out to Dr. Chagares again, and he was again told not to speak with the media, specifically The Cancer Letter, as per the hospital administration's instruction."

Because of Monmouth's public statements on "safety concerns," the hospital's leadership has an even greater responsibility to communicate with Chagares and his patients, UCSF's Redberg said.

"For a hospital to announce the safety concerns, the hospital is certainly, morally and ethically obligated to inform the patients, and state what the safety concerns are," Redberg said. "I cannot imagine a good reason why you would not follow up when you have concerns about safety. That would be all the more reason to do close and careful follow-up."

On Dec. 17, 2018, Chagares formally requested closure of the protocol.

"We are currently unable to perform robotic nipple-sparing mastectomies at Monmouth Medical Center and therefore do not have any patients who meet the inclusion criteria outlined to be enrolled in this observational study," Chagares wrote in the letter to Monmouth's IRB. "At this time, we are not able to enroll any patients and would like to close this study."

The hospital responded two months later, on Feb. 13, 2019.

"To advise you that the above referenced Study has been presented to the Institutional Review Board identified above, and the following action taken subject to the conditions and explanation provided below," Monmouth's Jaeger wrote in a letter from Arnold's office.

Below this statement, an annotation read: "IRB ACTION: Closed." There were no "conditions and explanation" provided.

How does this protect the patients?

"The IRB should be demanding that written communication occur to the subjects with an explanation of what's going on and what their rights are," NYU's Caplan said. "If someone is harmed or suffers harm later, and they have not had follow up, there is going to be significant liability.

"At this point in time, the standard of practice for recruiting subjects is to not only bring them in and discuss their options, but tell them when and what will happen if the study has to close prematurely."

Monmouth should have negotiated the shutdown of the study with Chagares, because as the surgeon and lead PI, he is responsible for the enrolled patients, Caplan said.

"That means the PI has to be fully informed," Caplan said. "We used to treat patients under the banner of 'subject,' and because we so eager to get people to come into research in oncology, but other areas, too, the notion has emerged in the past few years that people are to be treated as partners, co-equals, collaborators. This [hospital's] behavior isn't consistent with that."

These standards apply, whether patients are enrolled in a randomized clinical trial or an observational study, Caplan said.

"It doesn't matter, it applies to everyone," Caplan said. "The failure to have an exit strategy is unacceptable in 2019."

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LETTER FROM THE EDITOR

The path from a correction to an investigation of research conduct at Monmouth Medical Center

By Paul Goldberg

Our investigative story this week is an outgrowth of a correction.

Last summer, Monmouth Medical Center, a 500-bed hospital within the RWJBarnabas Health system, came to The Cancer Letter's attention when a breast surgeon there used a da Vinci robot to perform robotic nipple-sparing mastectomies on two patients, a woman with invasive breast cancer and a man with abnormal growth in his breast.

An April 5 story—reported and written by Matthew Bin Han Ong—was an installment is his years-long investigation of minimally invasive surgery, which includes power morcellation, laparoscopic procedures and robotic surgery (The Cancer Letter, How Medical Devices Do Harm).

The Monmouth story was worth doing, because minimally invasive technology often proliferated based on studies that didn't consider long-term cancer-related endpoints. Now, we see that while patents show short-term satisfaction with their minimally invasive surgeries, there are also reports of diminished survival in some settings, when compared to more conventional techniques (The Cancer Letter, Nov 2, 2018).

After hearing about robotically-assisted mastectomies at Monmouth and seeing local news reports, Ong wanted to know whether the surgeon, Stephen A. Chagares, performed these surgeries off-label. Did he have IRB approval? Did he have a protocol? If so, what was the architecture of the study? Was FDA asked to issue an Investigational Device Exemption?

In Ong's view—and in my view as the editor—that story had merit, regardless of the answers we received. We could segue from Chagares to an even more interesting set of questions about efforts to test robotic mastectomies in randomized trials, including one multi-institution study led by MD Anderson Cancer Center, and budding plans at the University of Pennsylvania. Also, we could explore why another top-tier institution—Memorial Sloan Kettering Cancer Center—has no plans to offer or study the procedure.

Why are surgeons experimenting with this equipment to perform mastectomies? Is it safe for the treatment or prevention of cancer? Is this a solution in search of a problem? How is FDA regulating this indication? Which endpoints and how much follow-up does the agency require to support issuance or expansion of a device's label?

Ong spent about seven months working on the robotic mastectomy segment of his series. Monmouth Medical Center officials didn't respond substantively to his questions, but in the process, he found a source who was clearly knowledgeable about the robotic mastectomies that were performed at the New Jersey hospital.

Of course, it would have been preferable to get answers on-record, but our job is to get information—often information people are trying to hide—and relying on sources who speak on background is a much-used tool of the trade.

The source went on background and told Ong that Chagares performed robotic mastectomy without a protocol. The source gave Ong additional information, most of it not flattering, which we didn't use, because the story was focused on devices and surgical outcomes, not Monmouth and Chagares.

I know the name of the source Ong relied on, and—based on information we later obtained—I have no doubt that the source was privy to information about Chagares's study. We confirmed this source's account with other confidential sources, but at Monmouth we didn't have the depth of connections we have at top-tier academic institutions. I was involved in the vetting, and I was unable to catch the incorrect information.

It was not an impressive protocol. It wasn't designed to test safety and efficacy, and sections of it were cut out of a randomized trial led by a group in Italy and scotch-taped together by the Monmouth IRB. But it did receive the board's final blessing. Chagares was clearly telling the truth.

I have been a reporter for about 40 years without ever encountering a situation where a source to whom I offered confidentiality used this protection to tell me something that wasn't true.

I made two decisions:

1. I decided that we will continue to honor our commitment to keep the source's confidentiality, even though the arrangement in this case went awry. However, one bad episode in four decades is a pretty good success rate. Generally, the benefits of confidential communication with sources outweigh the potential harms of a confidential source using this privilege to plant disinformation.

> The Monmouth story was worth doing, because minimally invasive technology often proliferated based on studies that didn't consider long-term cancer-related endpoints.

After the story was published, we received a miffed email from Chagares, who informed us that, contrary to our report, he had a protocol that was approved by Monmouth's IRB. We have since obtained internal documents and emails confirming that the protocol was designed to collect satisfaction data as well as cancer-related outcomes data associated with the robotic mastectomies at Monmouth.

2. After learning that we had relied on incorrect information, I decided to keep Ong's story package intact, instead annotating it to show what we have learned since.

You might call this a Bayesian correction. The Monmouth imbroglio was now a part of the story. We decided to keep digging, with me doing some of the reporting. We would take advantage of what we learned and change the course of the investigation accordingly.

The internal documents we obtained portray Chagares as a busy surgeon who fully trusts Monmouth's IRB to guide him away from the cliffs. He plays by the rules, even as the IRB spectacularly botches the study design, informed consent forms, and the conduct of the study. He stays silent even as hospital officials place a moratorium on the procedure without telling him what their "safety concerns" were.

Had Chagares disregarded the hospital's directives and spoken with Ong as he reported the initial story, that story would have been different. There would have been no corrigendum—or this investigative piece.

After annotating Ong's initial story, on April 7 and 8, we submitted 32 questions to top officials at Monmouth Medical Center. On May 30, we submitted another set of 32 questions.

Too often, journalists go away after being blown off by institutions that are engaged in unsavory behavior. The Cancer Letter doesn't go away. And—this is a heads up to the folks at Monmouth Medical Center—we aren't done.

Can another cancer protocol as misguided as this one be approved by the Monmouth IRB? Probably not, because going forward, all cancer-related clinical trials in the RWJBarnabas Health system are required to go through scientific and feasibility review at Rutgers Cancer Institute of New Jersey prior to IRB review.

And yet, there is no such thing as a trivial failure to protect patients from unreasonable research risks and unethical conduct. Every IRB failure—and this is a big IRB failure—is an opportunity to learn.

The Cancer Letter will be here to monitor this learning process.

Q & A

Fotopoulos spoke with Matthew Ong, a reporter with The Cancer Letter.

CONVERSATION WITH THE CANCER LETTER

Fotopoulos: Monmouth Medical Center told us to not follow up with robotic mastectomy patients

Nicholas Fotopoulos
Research coordinator for Stephen Chagares
Undergraduate student, Princeton University

> In the initial consultation meeting, the question of whether an IDE was necessary came up, and we were advised that an IDE was not required. The answer to the question became 'Not Applicable' on the application from there forward.

As the team lead by surgeon Stephen Chagares prepared a protocol for robotically-assisted mastectomy, the Institutional Review Board at Monmouth Medical Center provided guidance "every step of the way," said Nicholas Fotopoulos, a research coordinator and an undergraduate at Princeton University in his sophomore year.

Fotopoulos was recruited by Chagares early in 2018 to assist him with preparing a research protocol to study the use of a robotic surgical device in nipple-sparing mastectomy procedures.

In the course of reporting a previous story April 5, an inside source informed this reporter that Chagares performed robotic mastectomy on patients without a protocol and without oversight. This, The Cancer Letter later learned, was inaccurate.

"Not only did the RNSM clinical trial get approved under the oversight of the IRB and Dr. Toesca, but the IRB committee itself worked with us pretty much in every step of the way in order to design the protocol," Fotopoulos said. "We wanted to make sure we did everything correctly. "Monmouth Medical Center, and the IRB committee, specifically, was with us every step to make sure that this protocol was as it should be."

Fotopoulos spoke with Matthew Ong, a reporter with The Cancer Letter.

Matthew Ong: How would you describe your involvement with Dr. Stephen Chagares, Monmouth Medical Center, and their work on robotic mastectomy? What was your role in the creation or administration of the protocol?

Nicholas Fotopoulos: I was part of the procedure pretty much from the start to where it is right now. I've been shadowing Dr. Chagares and we both went to Milan to observe the procedure with Dr. [Antonio] Toesca.

Dr. Toesca taught Dr. Chagares how to perform an RNSM. From there, we came back to the United States with the intention of bringing the procedure here. I was listed as a research coordinator on the clinical trial, and that gave me a whole host of responsibilities that I was involved in. I prepared the IRB documents for RNSM to gain IRB approval.

Those documents, and what was necessary, came from the IRB committee at Monmouth Medical Center. The IRB committee had their own input on revisions multiple times throughout the admission process. We made every modification they requested.

Did Dr. Chagares perform the procedures under a trial or study protocol that was approved by Monmouth?

NF: Yes. The clinical trial was approved by the IRB committee unanimously—8-0. I was there for that.

We consulted with and shared the patient's medical records with Dr. Toesca to confirm that our first patient would be an appropriate surgical candidate for RNSM. He confirmed she was an appropriate candidate and would have included her in his trial if he had consulted with her in Italy.

What was the nature of the trial or study? Could you describe the design, target enrollment, and endpoints?

NF: It was an observational clinical trial, 10 years in total for 50 patients. Enrollment ends at the year five point, so we can follow up for the next five years into that final test year.

The study included cancer patients and high-risk patients who were candidates for traditional skin-, nipple-, and areola-sparing mastectomy. We mimicked Dr. Toesca's clinical trial for design, target enrollment, and endpoints.

I also noticed that the study was supposed to remain active for 10 years, presumably to allow for long-term follow up?

NF: These patients, as per the study, were to return to Dr. Chagares' office for follow up four times during the first year and then semi-annually for the following four years in order to assess how they're doing.

We were also monitoring oncologic outcomes to make sure that, with regular follow up with Dr. Chagares, these patients were staying healthy, they were pleased with their cosmetic outcome, the cancer wasn't returning, and the oncologic outcomes were the same or better than standard surgery.

How are the endpoints similar (or different) to the Italian RCT led by Dr. Antonio Toesca?

NF: The only difference was that ours is a single arm clinical trial. We eliminated the part that prevented patients from choosing RNSM.

The idea was to also track, through patient follow ups, any data related to adjuvant chemotherapy, radiation,

hormone therapy—anything that may have been in the patient's medical regimen prior to the procedure, or may have been necessary after the procedure, which is standard to current mastectomy procedures as well.

It appears that the IRB was in charge of the protocol design, from start to finish. Is this true? Who else provided oversight?

NF: Not only did the RNSM clinical trial get approved under the oversight of the IRB and Dr. Toesca, but the IRB committee itself worked with us pretty much every step of the way in order to design the protocol. We wanted to make sure we did everything correctly.

We were assigned a point person at Monmouth who is involved in the IRB who constantly went back and forth with us. Through this designated contact, Monmouth Medical Center made a multitude of direct edits to the protocol, consent, and other accompanying documents until they deemed them satisfactory.

Monmouth Medical Center, and the IRB committee specifically, was with us every step to make sure that this protocol was as it should be.

Did Dr. Antonio Toesca serve as a proctor for Dr. Chagares? Was Dr. Toesca's involvement approved by the hospital?

NF: Yes. It was assumed that a proctor would be needed because it was a new procedure. Even Dr. Chagares, when he did his first hernia robotic procedures five years ago, had a proctor there for his first time.

It's a typical procedure to have a proctor come in for something that's relatively new to a surgeon, so it was something that the hospital signed off on, wanted him there, especially after we said we got this procedure from Dr. Toesca.

We wanted him to be the proctor. Dr. Chagares would never have performed the procedure without a proctor.

Based on what you know, was Dr. Chagares instructed by the hospital administration not to speak with The Cancer Letter? Why?

NF: As I recall, after the first robotic mastectomy procedure of September 2018, Dr. Chagares initially presented his patient at a breast conference at Monmouth Medical Center and at a second breast conference in Pennsylvania.

When you first reached out, Dr. Chagares referred to the hospital administration, and they said there were very strict media guidelines for IRB clinical trials and he was told not to speak with the Cancer Letter.

I believe you reached out to Dr. Chagares again, and he was again told not to speak with the media, specifically The Cancer Letter, as per the hospital administration's instruction.

Ultimately, was the hospital responsible for determining whether the study required IDE review by FDA? What was the hospital's decision?

NF: The hospital gave us a checklist of everything you need for the protocol to be approved, and one of those items was an IDE. In the initial consultation meeting, the question of whether an IDE was necessary came up, and we were advised that an IDE was not required. The answer to the question became "Not Applicable" on the application from there forward.

What were the hospital's initial concerns that led to the splitting of the study? I.e. only non-cancer patients were subsequently allowed to be enrolled to the protocol?

NF: Shortly after the first mastectomy, Dr. Chagares received a call from the hospital to separate the current clinical trial into two research groups—cancer patients and risk-reducing/non-cancer patients. There wasn't anything alarming about this request.

Monmouth Medical Center confirmed via email that we would pause the cancer patient trial until the new protocol was submitted, but the non-cancer patient clinical trial would remain intact and active. We got the impression that they just wanted the two separated for logistical/reporting purposes.

When the hospital decided to end the study in its entirety and place a moratorium on the procedure, how were you and Dr. Chagares's team informed of the decision? A patient had reached out and said she never received an explanation from the hospital. Did administration officials provide written justification for the moratorium?

NF: In November 2018, Dr. Chagares' surgical coordinator tried to schedule an RNSM procedure for a risk-reducing patient. That was the first verbal notification where the hospital informed our group that the procedure was put on hold, without any written confirmation.

The patient had to be informed impromptu and without written confirmation as to why they could not receive the procedure they wanted to have. Dr. Chagares had to explain this to the patient without hospital correspondence, informing them that there were safety concerns with the current procedure.

The nurse manager then confirmed the coordinator could not schedule any RNSM. Dr. Chagares sent multiple emails and put out calls to the hospital. They confirmed via telephone to Dr. Chagares that all RNSM's are completely halted, with no specifics as to why.

I received from that point a phone call from Dr. Chagares informing me what he had just been told, he said the hospital was concerned by a letter from Dr. Hooman Noorchasm, and I also read the news and the article that was published in the Asbury Park Press. To my knowledge, no one has received written notification of that decision by the hospital and we did not receive a copy of Dr. Noorchasm's letter.

With every change to a clinical trial, typical protocol dictates that you should be given written notification of the change. We were never provided with any written official communication as to why a complete moratorium was placed on the procedure, or why the protocol was initially split between the two patient populations.

Have patients been notified that the trial was shut down?

NF: Yes, only by Dr. Chagares. He has a policy of full disclosure with all details with his patients.

The patients received no communication from the hospital. I think you can see from the emails from the patient that reached out to you that they were frustrated, knowing very little about the reason behind any of this, wanting to undergo RNSM, and completely being shut off from that opportunity.

Based on documents obtained by The Cancer Letter, on April 15, the hospital instructed Dr. Chagares to stop "collection of any additional data on the subjects already enrolled." Does this go against the design of the trial and any follow-up that was promised to the patients?

NF: Yes. That was part of the plan, as we said, with the clinical trial, to follow up regularly as Dr. Chagares does with all of his patients. We were told to not follow up with those patients, no additional collection of data. That's greatly concerning. It's definitely a threat to patients' health.

Despite these instructions, Dr. Chagares is still following the patients very closely, as he does with all his mastectomy patients, as is the medical standard of care.

If Dr. Chagares were to follow through with those instructions, collect no more data, to not observe the health outcomes of your patients—that would be totally inexcusable.

For patients to see that the hospital is saying, "We're not going to follow up with you anymore, we want to cut you off," the patients were largely frustrated that all this was happening and there was so much confusion about it.

There was very little transparency as to why certain things were happening. I believe that not following up with the patients, as per the protocol they signed up for, would be completely wrong.

Does this moratorium on follow-up go against standard practice and principles of medical ethics?

NF: Looking back now, I experienced Monmouth Medical Center being very enthusiastic about RNSM. They were instrumental in the extensive IRB clinical trial approval process. With all the work that went into development of this clinical trial to obtain their IRB approval, to be very quickly halted—it doesn't make sense.

To see the hospital behaving like this, it alarms me that there's a potential for a different administrative goal in light of The Cancer Letter's article. I was shocked to read the inaccuracies. I can only conclude that "Multiple sources with direct knowledge of the situation who spoke on the condition that their names would not be used" lied to you about Dr. Chagares.

So, I'm at a loss to explain how this is actually happening or what's going on behind the scene, because we just don't know, but it seems more of an orchestrated hospital administrative agenda behind all of this.

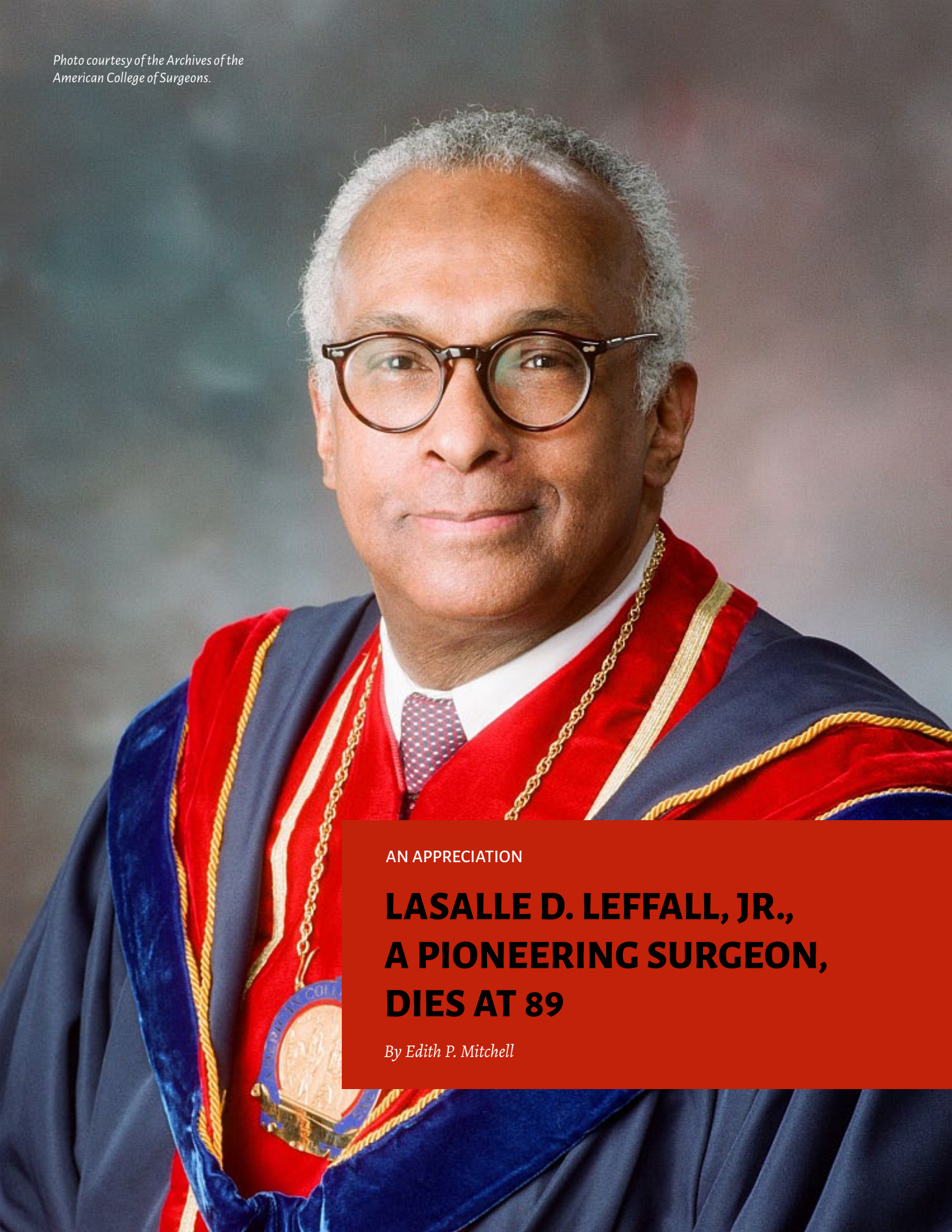

Photo courtesy of the Archives of the American College of Surgeons.

AN APPRECIATION

LASALLE D. LEFFALL, JR., A PIONEERING SURGEON, DIES AT 89

By Edith P. Mitchell

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It is with great sadness that I share the recent passing of an oncology icon, Dr. LaSalle D. Leffall, Jr. As said by Dr. Wayne Frederick, a mentee, surgical oncologist, and president of Howard University, "He was a surgeon par excellence, oncologist, medical educator, civic leader, and mentor to me and so many others."

I, too, was fortunate to be mentored by Leffall, who not only taught me about cancer, but also how to deliver the message to others. He was never too busy to talk and provided his cell phone number for me to call whenever I needed.

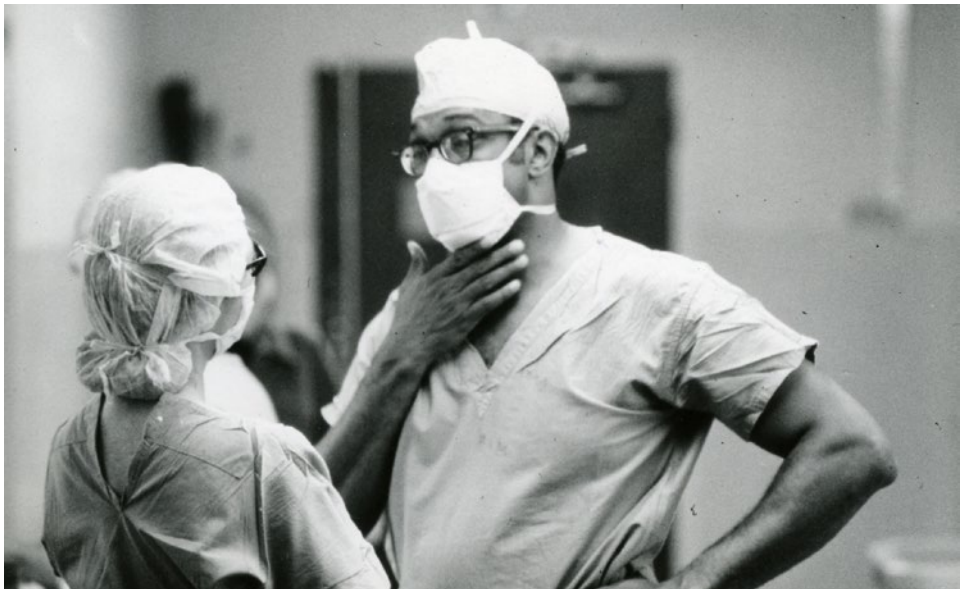
LaSalle D. Leffall, the Charles R. Drew Professor of Surgery, Howard University College of Medicine, was born May 22, 1930, in Tallahassee, FL, but grew up in Quincy, FL, attending its public schools. In 1948, at the age of 18, he was awarded a B.S. with greatest distinction (summa cum laude) from Florida A&M College.

In 1952, he received an M.D. degree from Howard University College of Medicine, ranking first in his class. Completing his surgical training at Freedmen's Hospital, now Howard University Hospital, in 1957, he then took a surgical oncology fellowship at Memorial Sloan Kettering Cancer Center from 1957 to 1959.

He began his military career at the rank of captain, M.C., serving as chief of general surgery at the U. S. Army Hospital in Munich, Germany from 1960 to 1961. He received an Honorable Discharge in December 1961 with the rank of Major. His membership on Howard's faculty began in 1962, progressing to professor and chairman of the Department of Surgery in 1970—a position he held for 25 years.

He served as a visiting professor and guest lecturer at more than 200 medical institutions in the U.S. and abroad. He also authored or coauthored more than 150 articles and book chapters.

Throughout his 55 years on the faculty, he taught approximately 6,000 medical students of the 9,000 graduates since the medical school's founding in 1868. He also helped train nearly 300 general surgery residents of the 360 residents trained since the program's inception in 1936.



LaSalle D. Leffall, Jr. in the O.R. in the 1960s. – *Photo courtesy of Howard University Archives*

His professional life has been devoted to the study of cancer, particularly among African Americans. In 1979, as national president of the American Cancer Society, he launched a program on the challenge of cancer among Black Americans. He paid special attention to the increasing incidence and mortality of cancer in this population group and its implications for similar studies in other racial and ethnic minorities. It was the first program of this type in the nation, addressing the problems of cancer health disparities. Today, practically all oncology groups have disparity issues as one of their major priorities.

He was the first African American president of the following organizations: American Cancer Society, Society of Surgical Oncology, Society of Surgical Chairmen, Washington Academy of Surgery, and the American College of Surgeons.

He was also a member of the Institute of Medicine at the National Academy of Sciences. He is past president of the Society of Black Academic Surgeons and past chair of the Surgical Section of the National Medical Association.

He has received 14 honorary degrees from American universities, including: Georgetown University, University of Maryland, Florida A & M University, Meharry Medical College, Clark University, Morehouse School of Medicine, Howard University, University of the South, Albany Medical School, Amherst College, Lafayette College, Thomas Jefferson University, Princeton University, and Colgate University.

He is an Honorary Fellow of the following: The West African College of Surgeons, the Société Internationale de Chirurgie, College of Surgeons of South Africa, the Royal College of Surgeons of

Canada, the Deutsche Gesellschaft fuer Chirurgie (German Surgical Society), and the Royal College of Surgeons of England.

He was named the first Charles R. Drew Professor in 1992. The LaSalle D. Leffall, Jr. Surgical Society was formed in 1995 and the Leffall Chair in Surgery was established in 1996. He received the first Heritage Award from the Society of Surgical Oncology in 2001. The biennial LaSalle D. Leffall, Jr. Cancer Prevention and Control Award is sponsored by the Intercultural Cancer Council and the MD Anderson Cancer Center.

The Pugh-Leffall Surgical Educational Fellowship—sponsored by a grant from Carla Pugh, HUCM '92, and former surgical resident—is awarded to outstanding sophomores with an interest in surgery and surgical research. The LaSalle D. Leffall, Jr. Komen Fellowship in Health Disparities was established by the Susan G. Komen Breast Cancer Foundation in 2006. The LaSalle D. Leffall, Jr., Learning Resource Center—made possible by a major contribution from Stephen Rush, HUCM '83, on behalf of his class—was established in the College of Medicine in 2006.

The Howard University Press published his memoirs, *No Boundaries – A Cancer Surgeon's Odyssey* in 2005 and *Equanimity Under Duress: Calmness and Courage in the Battle Against Cancer* in 2014. He is also coauthor of the Howard University College of Medicine sesquicentennial publication *Education, Excellence, and Exemplars*, which was released in 2017.

The 2009 Howard medical school class members named him as Outstanding Faculty Member during their Long White Coat Ceremony. Other honors from that year include: Inaugural Recipient Charles R. Drew Award of Excellence from Charles Drew School of Medicine and Science in June; and Special Recognition and Commendation as Chair, C-Change from 1998-2009, given at annual meeting, Kennebunkport, Maine later that same month. An invitation from President George H.W. Bush was sent on occasion of his 85th birthday.

He was chair of the Susan G. Komen Breast Cancer Foundation from 2002 to 2007 and 2011 to 2012 and chair of the President's Cancer Panel from 2002 to 2011. In 2011, he received the W. Montague Cobb Lifetime Achievement Award from the National Medical Association. At the Walter Reed Army Medical Center, he received the Commander's Award for Public Service, for his work as the principal civilian consultant to the General Surgery Service for 30 years, from 1970 to 2000.

Howard University president Sidney A. Ribeau appointed him interim senior vice president and executive dean for health sciences in August 2011 and interim provost and chief academic officer in December 2011. He served in these positions until 2012.

This latter appointment combined the previous positions of provost and senior vice president for health sciences into a single senior academic leader position reporting directly to the president. He served in this position until July 2012. He continued as the Charles R. Drew Professor of Surgery, and, at the time of his passing, he was senior advisor to Howard University President Wayne A. I. Frederick, one of his former students.

> The great heights reached by Dr. Leffall never kept him from being accessible to students, patients, and staff in a manner that was marked by unconditional love and selflessness.
>
> *– Wayne A. I. Frederick*

Wayne Frederick, Howard University president, with LaSalle D. Leffall, Jr., seated.
– Photo courtesy of Howard University Archives

"The great heights reached by Dr. Leffall never kept him from being accessible to students, patients, and staff in a manner that was marked by unconditional love and selflessness," Frederick said. "He was a good listener, slow to give or take offense and always encouraging others to find the broader lesson in seemingly quotidian situations."

Edward Cornwell—who was also mentored by Leffall, is currently the LaSalle D. Leffall, Jr., M.D. Professor and Chairman of Surgery at Howard University College of Medicine and surgeon-in-chief at Howard University Hospital—provided me the most vivid description of his interactions with Leffall as a mentor and teacher.

"His towering intellect made each interaction edifying. In one moment, he might correct your grammar before pivoting to discuss some complex idea or concept. Dr. Leffall might even share a few thoughts in German, given his fluency in the language," said Cornwell.

"The breadth of his academic pursuits was nothing short of awe-inspiring. The legions of human beings impressed, inspired, and improved by Dr. Leffall transcends surgery, medicine, or barriers of language, race, class, politics, or geography. He was a lover of life, lived his to the absolute fullest, and attacked its vicissitudes with a hallmark discipline that he always displayed and that became emblematic of him and his iconic mantra: Equanimity Under Duress."

Even after retiring from surgery, Leffall remained on the faculty as a lecturer and resource at Howard University. He continued contributing to the National Medical Association, as well as other organizations.

LaSalle D. Leffall's impact on oncology, and other areas of medicine, in the United States and globally is well-recognized and he will be forever remembered as the ultimate physician, teacher, mentor, administrator, public servant, advocate, and friend.

I am sure the entire oncology community joins the Howard University community in extending our sincerest sympathies to Dr. Leffall's wife, Ruth, Dr. Leffall's son, LaSalle Leffall, III also known as "Donney," his sister Dolores C. Leffall, their family, friends, his staff, and mentees. We will keep them in our hearts during this difficult time.

> "The breadth of his academic pursuits was nothing short of awe-inspiring. The legions of human beings impressed, inspired, and improved by Dr. Leffall transcends surgery, medicine, or barriers of language, race, class, politics, or geography."
>
> *– Edward Cornwell*

The author is clinical professor of medicine and medical oncology in the Department of Medical Oncology, director of the Center to Eliminate Cancer Disparities, and associate director of diversity affairs at Sidney Kimmel Cancer Center at Jefferson, as well as the 116th president of the National Medical Association.

AN APPRECIATION

Leffall, one of five surgeons to serve as president of two ACSs, the American Cancer Society and American College of Surgeons

by LaMar S. McGinnis

We have known a giant—physically, mentally, fraternally, socially, professionally, ethically, spiritually. Now he is gone, but will be long remembered and loved.

Growing up as the son of educators in the segregated South, LaSalle Leffall was taught that education and character were key, and he learned that lesson well. He pursued excellence successfully in so many arenas, and his character was never questioned. This pursuit of excellence led him to become a physician, a surgeon, an oncologist, and a consistent, tenacious leader.

Being first became commonplace for him: the first African American president of the American Cancer Society (1994-1995), the first African American member of the Southern Surgical Association, the first African American president of the American College of Surgeons (2009-2010), one of five surgeons to serve as president of the two ACSs—and more, are among his many accomplishments.

A master orator with the memory of an elephant, LaSalle would hold his audience spellbound as he told stories, used extensive quotations, and made emphatic points, all without notes or prompters. Driven always by principle—never blustery, always emphatic—he would successfully sway opinion in his ongoing effort to right longstanding wrongs and to enhance understanding. His knowledge and ability in surgery, oncology, and health policy was prolific. He was ever-responsive. His counsel was in wide demand, even to some presidents of our nation. He was a devoted family man, and he and Ruthie were an ever present and enviable team, like salt and pepper.

LaSalle D. Leffall, Jr. as a young surgeon in the 1960s. – *Photo courtesy of Howard University Archives*

LaSalle was a charismatic leader during a time of sea change in our nation. So often it seems to occur in our good land and accrues to our general benefit—the right man at the right time.

He had friends in all spheres of influence and activity, including some of the giants of jazz. They taught him the importance of the "grace note." It is with a grace note that he has left us.

Thank you, my old and true friend.

The author is an adjunct professor of surgery at Emory University School of Medicine.

IN BRIEF

Ohio State receives $11M NCI grant for Appalachian cervical cancer prevention

A public health initiative aimed at preventing cervical cancer in at-risk Appalachian families from Ohio, Kentucky, Virginia, and West Virginia is underway with support from an $11 million NCI grant to Ohio State University Comprehensive Cancer Center–Arthur G. James Cancer Hospital and Richard J. Solove Research Institute.

The OSUCCC–James is collaborating with 10 health systems throughout Appalachian Ohio, Kentucky, Virginia, and West Virginia to conduct this research, in partnership with the University of Kentucky, West Virginia University, and the University of Virginia.

Led by Electra Paskett, leader of the OSUCCC–James Cancer Control Research Program, this initiative builds on a history of collaborative research and community partnerships.

The effort will focus on reducing the burden of cervical cancer in at-risk Appalachian communities by specifically targeting the primary causes of cervical cancer: tobacco smoking, human papillomavirus infection, and lack of cervical cancer screening.

The project will implement and test the effectiveness of an integrated cervical cancer prevention program consisting of three interventions: nicotine replacement therapy and smoking cessation counseling services, a method of at-home HPV screening, and a medical practice-based intervention to improve HPV vaccination rates among patients age 11—26 years of age in Appalachia-based health centers.

"This region has one of the highest rates of cervical cancer and cervical cancer deaths in the United States. We know that smoking tobacco products, HPV infection, and lack of timely cervical cancer screening play a significant role in these exceptionally high rates," Paskett, the Marion N. Rowley professor at Ohio State University College of Medicine and College of Public Health, said in a statement.

"In the Appalachian area of the United States, vaccination rates are still far below the national average, and studies have shown the HPV vaccine is effective for not only reducing rates of cervical cancer but also other forms of HPV-linked cancers that are on the rise," said Paskett.

"These health disparities in underserved communities are not new—they are long-standing and must be addressed in a systematic, sustainable way. We hope to do just that through the type of intentional community collaboration established in this study."

ACS receives $1.99M grant for sub-Saharan African patient navigation initiative

The American Cancer Society has been awarded a $1.99 million, five-year grant to improve support and access to care for people living with cancer in low-and-middle-income countries, particularly sub-Saharan Africa. This funding will help ACS expand patient navigation to countries with a growing burden of cancer.

The grant was awarded by the Merck Foundation.

More than 70% of the nine million cancer-related deaths worldwide are in resource-limited settings, where patients face many barriers to timely diagnosis and high-quality cancer care.

With support from the foundation, ACS will fortify its patient navigation program in Kenyatta National Hospital, a national referral hospital in Kenya, and adapt it for The Uganda Cancer Institute, a high need facility in Uganda which serves about 200 patients daily.

This grant is a first step toward expansion of patient navigation programs. As part of this, ACS said it will create a comprehensive guide and toolkit to develop and implement patient navigation programs, designed specifically for health facilities in low- and middle-income countries.

"Uganda has a population of 43 million, but there are only 20 oncologists in the entire country," Jackson Orem, executive director of the Uganda Cancer Institute, said in a statement. "That's one of the reasons why patient navigators are so important in helping patients manage the day-to-day challenges that prevent them from receiving care and empowering them to seek treatment and stay in care."

ACS will work with the Rollins School of Public Health at Emory University to evaluate the implementation of the patient navigation programs in Kenya and Uganda as well as the pilot of the program design guide and implementation toolkit.

Seewaldt and Buermeyer awarded grand prize from the Global Challenge to Prevent Breast Cancer

The Global Challenge to Prevent Breast Cancer has awarded:

- The Grand Prize (Researcher Category) to **Victoria Seewaldt**, professor and chair of Population Sciences at City of Hope, who, with Chris Sistrunk of the SoCAL STEM and Community Outread Team, proposed STEM education to help prevent breast cancer.

- The Grand Prize (Advocate Category) to **Nancy Buermeyer**, senior policy strategist at Breast Cancer Prevention Partners, who, with co-author Janet Nudelman, advocates reducing emissions at major ports to lower breast cancer risk.

- In addition to the two Grand Prize winners chosen by a judging committee of experts and advocates, those in attendance and watching online also had their say, voting on an Audience Choice Award. The winner, **Michele Atlan**, vice president at the Breast Cancer Care and Research Fund, proposed a novel way to repackage natural ingredients to aid prevention efforts.

Started by the California Breast Cancer Research Program last fall, the Global Challenge was designed to uncover transformative prevention research ideas, and address the staggering statistic that, despite treatment advancements, people continue to be diagnosed with breast cancer at rates that have remained essentially unchanged over the past three decades.

Finalists were selected from dozens of applications that were submitted to the Global Challenge and competed at the Idea Showcase and Competition in San Francisco.

The ideas presented at the Global Challenge Idea Showcase and Competition will inform more than $15 million in funding that CBCRP will devote to breast cancer prevention research over the next five years.

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THE CLINICAL CANCER LETTER

Project ECHO brings specialized knowledge to rural providers

CONVERSATION WITH THE CANCER LETTER

Oliver Bogler
Chief operating officer, Project ECHO

Lucca Cirolia
Program planning manager, ECHO Cancer Initiative

> This is why ECHO was created; we will never train enough specialists—particularly these extreme specialists—to meet the needs of the world. We have to find more innovative ways of getting that expertise to everyone who needs it.

– Oliver Bogler

Q & A

Bogler & Cirolia spoke with Claire Dietz, a reporter with The Cancer Letter.

Project ECHO, a service that provides physicians in rural areas with access to multidisciplinary expertise, will soon announce partnerships with four cancer centers—Dana-Farber Cancer Institute, Mayo Clinic Cancer Center, University of New Mexico Comprehensive Cancer Center, and Yale Cancer Center.

Founded in 2003 by Sanjeev Arora, a hepatologist based out of Albuquerque, NM, Project ECHO is based at the University of New Mexico School of Medicine. The oncology arm of the project, the ECHO Cancer Initiative, reaches physicians in 10 countries through 45 hubs.

The project's name stands for Extension for Community Healthcare Outcomes, connects rural providers to specialist teams at academic medical centers. It has long-standing collaborations with four NCI-designated cancer centers: MD Anderson Cancer Center, The University of Chicago Medicine Comprehensive Cancer Center, Vanderbilt-Ingram Cancer Center, and the University of Colorado Cancer Center.

"Because cancer is a very complex disease, and often a combination of diseases, it is essential that Cancer ECHO hub teams are also multidisciplinary," said Lucca Cirolia, program planning manager at ECHO Cancer Initiative, to The Cancer Letter. "For example, if you're a physician assistant who is dealing with a survivorship plan adherence issue, you can use ECHO to discuss the case with a social worker, a nutritionist, a pharmacist, and a psychiatrist, as well as an oncologist, about the side effects your patient is experiencing."

Using teleconferencing systems, physicians are able to call specialists and discuss diagnoses and treatment options for their patients.

ECHO collaborations have a "hub-and-spoke" design, with multidisciplinary expert teams at the hubs and community-based providers in underserved communities at the spokes, said Oliver Bogler, ECHO's chief operating officer.

"[They] use case-based presentations to share best practices, and do group problem-solving," Bogler said to The Cancer Letter. "Short didactics are usually also part of an ECHO session, and over time, through what we call tele-mentoring, the spoke providers become knowledgeable and empowered. They feel confident to start treating patients they had not previously treated."

The original ECHO hub in New Mexico was focused on hepatitis C. Over the years, the model has expanded to other areas of medicine, including oncology.

In 2003, there were approximately 28,000 cases of hepatitis C in New Mexico—the fifth largest state in the U.S.—but only two treatment facilities where patients could access care, Bogler said.

"At the time, hep C was treatable with a fairly complex regimen of chemo that caused notable side effects," Bogler said to The Cancer Letter. "It was not an easy treatment to manage—a 75% cure rate, and so was certainly effective enough for him to want to bring it to people."

In 2011, a study published in the New England Journal of Medicine describes Project ECHO's impact on underserved communities.

"The results of this study show that the ECHO model is an effective way to treat HCV infection in underserved communities," the authors concluded. "Implementation of this model would allow other states and nations to treat a greater number of patients infected with HCV than they are currently able to treat."

ECHO is a department of the School of Medicine at the Health Science Center of the University of New Mexico. Operationally, ECHO consists of two components:

The first part runs over 30 ECHO programs with and for UNM faculty for the benefit of the people of New Mexico and beyond. For this, ECHO receives funding from the State of New Mexico.

The second aspect is focused on replicating the ECHO model with partners both in the U.S. and around the world. This is entirely "soft-funded" by grants from foundations and government.

Some of these funders include:

- General Electric Foundation;
- Robert Wood Johnson Foundation;
- Bristol-Myers Squibb Foundation;
- Merck Foundation;
- Department of Defense—Defense Health Agency;
- Health Resources and Services Administration;
- Centers for Disease Control and Prevention;
- Co-Impact.

"For replication in cancer, we rely on the grant from Bristol-Myers Squibb Foundation which is $10 million over five years and started in 2017," Bogler said. "Because of the generous support of our funders, we are able to offer our training and support to our hub partners at no charge, and so there is neither a training fee nor any kind of annual fee to be an ECHO partner or to use the ECHO model."

ECHO has now become integrated into several international governments' systems, including Ontario's Ministry of Health. In 2016, President Barack Obama signed the ECHO Act, which directed the Department of Health and Human Services to not only study ECHO, but also report their findings to Congress.

"The assistant secretary for planning and evaluation at HHS worked with the

RAND Corporation and others to produce the report, which recognizes the significant momentum for the adoption of ECHO and noted the need to expand the evidence base," Bogler said. "We agree, especially as the portfolio of ECHO programs diversifies. Now, there's discussion around opportunities to fund more research on ECHO."

Across the board, Project ECHO has 300 hubs for more than 100 diseases and conditions in 35 countries. The project now has more than 650 programs.

"ECHO is not a consult service that you access occasionally; it is a long-term learning community that increases capacity and improves care, over time," Bogler said. "Improved learning of the entire ECHO program community is the larger goal, and the advice for a given patient is one key component of how that is done. Eventually, the spoke providers can reach a point where they don't need advice to manage their patients for the condition in question."

Bogler and Cirolia spoke to Claire Dietz, a reporter with The Cancer Letter.

Claire Dietz: What are the origins of Project ECHO?

Oliver Bogler: The program was developed by Dr. Sanjeev Arora here at the University of New Mexico. He's a gastroenterologist, and he started Project ECHO about 15 years ago. He came to New Mexico from Boston, where he had trained, and he was interested in treating hepatitis C. He noted that there were 28,000 people thought to have hepatitis C in the state [in 2003], but that there were only two places where they could get care.

At the time, hep C was treatable with a fairly complex regimen of chemo that caused notable side effects. It was not an easy treatment to manage—a 75% cure rate, and so was certainly effective enough for him to want to bring it to people.

Dr. Arora initially sent the treatment guidelines to rural providers. However, New Mexico is the fifth largest state geographically, with only about 2.09 million people, and the majority of the state is medically underserved. A third of the people in the state are supported by Medicaid. So, it is a difficult environment in which to provide complex care. And unfortunately, when he shared the guidelines, providers did not take on the care of hep C. It was too complex and they didn't feel empowered.

So, Dr. Arora created the first ECHO community. ECHO communities are by their nature relatively small. They're highly social, they have a hub-and-spoke architecture with a multidisciplinary expert team at the hub, and spokes with community-based providers, typically from underserved areas, whether rural or urban.

They meet synchronously, supported by real-time teleconferencing on the Zoom platform, use case-based presentations to share best practices, and do group problem-solving. Short didactics are usually also part of an ECHO session, and over time, through what we call tele-mentoring, the spoke providers become knowledgeable and empowered. They feel confident to start treating patients they had not previously treated.

That's what happened in the original hepatitis C community, and ultimately the capacity for care for this disease increased about fivefold in New Mexico.

And Dr. Arora's wait time went from eight months to two weeks. He was able to see the patients that really needed him, and much sooner than he might otherwise have been able to. Before ECHO, patients would often present with advanced stage disease, partly because they had been so delayed in getting to him, because it was hard for them to travel, take off time from work, and for other reasons that are social determinants of health. After ECHO, that certainly changed.

So, that is the story of the original ECHO community, which is still going strong today. It still meets once a week on Wednesdays for 90 minutes. But Dr. Arora quickly understood from this work that other people and other use cases might be a good fit for ECHO. When he published his experience in 2011 in a New England Journal paper, it brought attention to the model and initiated the formation of partnerships and ECHO's rapid expansion to where we are today.

So, kind of like grand rounds with specialty care providers?

OB: Yes, grand rounds in the traditional sense of presenting the medical problems and treatments of an individual patient for discussion, and not grand rounds in the sense of a lecture.

ECHO distinguishes itself from other forms of distance education. It's not a webinar, it's not an online course, it's not videos. ECHO is highly interactive. We believe that adult learning occurs best when focused on a real-world problem.

In medical ECHO, like in residency training, you look at a case, you present it to an experienced team of colleagues, they give you feedback, and everyone discusses. We talk about "All teach, and all learn" because it's very dynamic. ECHO breaks down learning hierarchies that typically exist in traditional education settings. We don't want "the professor and the student." We want people to interact as peers.

So, the community providers will meet with the hub experts and say, "My patient is presenting symptoms of what I think is probably hepatitis C, what do you recommend? What would be the best course of treatment?"

OB: Correct. Unlike in telemedicine, where the remote provider cares for the patient at a distance, in ECHO the provider does not change. ECHO is not a consult service that you access occasionally, it is a long-term learning community that increases capacity and improves care, over time.

Improved learning of the entire ECHO program community is the larger goal, and the advice for a given patient is one key component of how that is done. Eventually, the spoke providers can reach a point where they don't need advice to manage their patients for the condition in question.

For example, in hepatitis C, we currently have over 35 active programs, rather than one big program. We don't want massive programs, but rather we want to achieve scale by replicating programs. ECHO programs are best when they are local, highly interactive, and social. If there are 300 spokes, then your turn to present a case will only come rarely and interaction will be difficult.

The cases are presented in an abstracted and de-identified form. The patient themselves never appear in the ECHO. Each ECHO community determines best disease-specific information that they feel they need to share in order to discuss the patient.

Is that to stay compliant with HIPAA protections?

OB: Yes, we do not share PHI—protected health information. We intentionally do not have PHI in our systems because of that. It's to protect people's privacy.

With rural cancer care, how have you seen ECHO improving access?

OB: In cancer, ECHO is seeing a lot of growing interest, some great partnerships are forming. However, for an ECHO community to work, the value proposition to the spoke participant has to be very clear.

So far, we've seen the most success in ECHOs focused on areas like palliative care. Similarly, there are programs in survivorship where specialist oncologists are collaborating with community providers to manage patients after their active-phase of treatment.

There are also great programs in tobacco prevention and cervical cancer prevention. We also have new ECHOs focused on increasing clinical trial access for underserved populations and managing the rapidly increased use of molecular genetic testing.

Lucca Cirolia: What makes ECHO so innovative is that the multidisciplinary nature of the hub team. In the original hepatitis C community, spokes were not just calling in to talk with Dr. Arora as the one hepatitis C expert. They called in to present their patient's case, receive advice from the network at large, and learn from the multidisciplinary team comprised of gastroenterologists, social workers, nurses, pharmacists, and psychiatrists.

Because cancer is a very complex disease and often a combination of diseases, it is essential that Cancer ECHO hub teams are also multidisciplinary. For example, if you're a physician assistant who is dealing with a survivorship plan adherence issue, you can use ECHO to discuss the case with a social worker, a nutritionist, a pharmacist, and a psychiatrist, as well as an oncologist, about the side effects your patient is experiencing.

I also want to emphasize the benefit of what we call the 'learning loop.' ECHO is really innovative because it's not just the spokes that are learning from the experts, but the experts are also learning from the community providers. And that's essential.

In New Mexico, we have a lot of cultural differences. It's really important that we are aware that a tobacco cessation plan may be more difficult for one of the tribes to implement, since they have traditional rituals that include tobacco. And the experts should be culturally sensitive when they provide recommendations to the network. This is the learning loop: the providers learn best practice from the hub team, and the experts learn about local community issues related to best practice adherence from the spokes.

One interesting ECHO program is the American Academy of Pediatrics. They're a super-hub, which means that they train other hubs in the ECHO methodology in addition to running their own ECHO programs. This network is running programs for HPV quality improvement. AAP has really taken ECHO to the next level, which means they not only have their spoke sites participate and learn as a community, but they become the experts and disseminate best practices to local providers across states like Arizona, New Jersey, and Oregon—a great example of force multiplication.

Additionally, the National Cancer Institute's Center for Global Health has three programs focused on disseminating best practices in national cancer control planning in the Caribbean, Asia Pacific, and Africa. The national cancer control plans have a special focus on breast and cervical cancer, as well. ECHO fa-

cilitates learning across communities where samples and tests can be compromised by distance and temperature. This knowledge can then be shared with other regions facing similar challenges.

OB: NCI's Africa program met recently and discussed cancer registries and heard presentations from Rwanda, among other countries. Very interesting to see a dynamic community of practice working together.

But to come back to your question, Claire, I would say ECHO focuses on moving knowledge and oftentimes, knowledge can be the missing piece. But technology and medicines are also critical. For example, in surgery, ECHO can bridge the gap between in-person visits, where there is hands-on training in the OR with colleagues; in-between visits, ECHO can be used to keep the conversation going.

MD Anderson has an ECHO program with Mozambique and Brazil that initially focused on cervical, it now includes breast and head and neck cancers. Physicians from Houston and Brazil visit Maputo [capital of Mozambique] periodically for workshops and then meet in ECHO sessions in-between.

It sounds like the focus in the Cancer Initiative right now is on expansion and getting people to have access to cancer-specific ECHOs?

OB: Yes, at the ECHO Institute at the University of New Mexico in Albuquerque, we're just 110 people. ECHO is entirely a partnership model, and we help partners learn ECHO and then launch their own programs. The institute is grant funded, which allows us to provide training and participation in ECHO with no charge. Today we have 300 partners, or hubs—it's growing weekly. Most have received formal ECHO training with us here in Albuquerque and some with our superhubs. MD Anderson is the superhub for oncology, and they are training many hubs in cancer.

[Across Project ECHO], these hubs are in 35 countries, running nearly 650 programs in about 70 different subject areas. Lucca and I focus on expanding the use of ECHO in cancer, thanks to a grant from the Bristol-Myers Squibb Foundation that supports our work in the United States and South Africa. We connect with potential partners, hold exploratory conversations, and if there's interest, we bring them in for training. Then we provide technical assistance and mentorship as they launch their programs. The hubs become very quickly self-sufficient and then run programs to meet their missions.

We also catalyze communication across programs. Lucca runs a monthly call, the Cancer Collaborative, where anybody participating in a cancer-related ECHO is welcome to join and then discuss areas of common interest. We're also moving toward building a stronger digital platform for the practice of ECHO and improved networking of ECHO participants.

Of the 70 NCI-designated cancer centers, we have eight either launched (The University of Chicago, University of Colorado, University of Texas MD Anderson Cancer Center and Vanderbilt-Ingram Cancer Center) or preparing to launch (Dana-Farber Cancer Institute, Mayo Clinic Cancer Center, University of New Mexico Comprehensive Cancer Center, and Yale Cancer Center). We welcome more conversations with community-based organizations and other groups focused on cancer, like patient advocacy groups.

LC: We mentioned MD Anderson and NCI, and we also partner with the American Cancer Society, American Society of Clinical Oncology, and the American Society of Clinical Pathology. There are also quite a few that are in pre-launch, but we did just learn that ASCO has launched their first program. Theirs is an interesting use case, where they are taking on the training component of the Union of International Cancer Control's City Cancer Challenge within four cities. Again, ECHO is being deployed alongside in-person training with the goal to more effectively treat and teach people best practice in cancer care delivery.

OB: We have a dashboard that shows the current footprint in cancer. And you can see all the individual programs. What are the numbers today, Lucca?

> "ECHO is really innovative because it's not just the spokes that are learning from the experts, but the experts are also learning from the community providers. And that's essential."
>
> *– Lucca Cirolia*

LC: We have a global interactive map that tracks all of our partners replicating the ECHO model, but this is specific just to cancer. [ECHO Cancer Initiative], has 45 hubs in 10 countries and each of the hubs has at least one active program, but many have more than that.

Across the 45 hubs, we have 70 programs. As Oliver mentioned, since 2003, when Dr. Arora started the first hepatitis C ECHO program, we have grown to about 35 hep C hubs globally. We're very happy that within about five years of diving into the cancer space, we've

been able to help partners launch 70 programs focused on cancer.

In five years?

LC: Yes, we are relatively new to cancer. MD Anderson, of course, has been a great partner and has been replicating the model in cancer since early 2014, but we're seeing an increased interest in the ECHO model for cancer care improvement.

We are seeing similar growth in other areas, including other infectious diseases, autism, mental health issues related to the opioid crisis, among others. There are some really interesting use cases outside medicine too, including a sheriff's department using ECHO for telementoring de-escalation tactics.

OB: We're moving rapidly outside of medicine. Education and civics are fast growing areas. ECHO can be used in many areas and we're excited about innovation from our partners. When you have scarce expertise, you have dynamic complexity, you have high social impact, then ECHO might be useful, and we're always excited when people come to us with new ideas.

I don't know how many cancer-related conversations Lucca and I are having, but there must be 20 or 30, at least, going on at the moment. Some of them with patient advocacy organizations and other kinds of programs. It's really exciting, I have to say.

What does the new legislative support for ECHO entail?

OB: Our ultimate goal is to have ECHO embedded in systems. We at the ECHO Institute are mostly catalysts, and whether that capability exists in five or 10 years is really not as important to us as if we've succeeded in getting ECHO into systems.

Internationally, that's been very successful. For example, in the state of Ontario, the Ministry of Health has adopted ECHO. In Namibia, in the country of Georgia, in India, national and regional governments have engaged. In these partnerships, either state or country-level ministries of health are the first to adopt ECHO and implement ECHO programs, because that's where it really shines, at the systems level.

In the United States, the health care system is organized a little differently, but we've also had some real success. In 2016, the ECHO Act was signed by President Barack Obama, and it directed the Department of Health and Human Services to study ECHO and report to Congress. They published their report in March of this year. The assistant secretary for planning and evaluation at HHS worked with the RAND Corporation and others to produce the report, which recognizes the significant momentum for the adoption of ECHO and noted the need to expand the evidence base. We agree, especially as the portfolio of ECHO programs diversifies. Now, there's discussion around opportunities to fund more research on ECHO.

In the course of ASPE's work, they uncovered that many parts of the federal government are supporting ECHO in different ways, including AHRQ, SAMHSA, CMS, IHS, and more recently the National Institutes of Health. For example, we are seeing an increased interest by Clinical and Translational Science Centers or members of NCI core grants to include support for ECHO.

In addition, New Mexico is operating under a Medicaid waiver to support ECHO programs, and Oregon and California are coordinating with their coordinated care and managed care organizations for this purpose.

Additionally, there was recent legislation in response to the opioid crisis where funding preference is given to health centers participating in ECHO programs, in recognition that the ECHO opioid programs are effective.

ECHO is also an educational methodology. You can deliver continuing education credits and certification credits through ECHO programs. Certification of programs is a service we offer at the institute, and we feel that such credits can be another incentive to participate in the ECHO community.

Did I miss anything?

OB: We welcome conversations with community-based cancer providers and others in the cancer space, because ECHO is a great way to share scarce expertise. ECHO was born in an academic medical center, so we are well connected to the academic cancer community through our comprehensive cancer center here at the University of New Mexico.

Before I joined ECHO, I worked at MD Anderson for 13 years, and learned about the hyper-specialization that is going on in cancer and in medicine broadly. The top specialists are getting more and more knowledgeable, but they are also focusing their specialization.

This is why ECHO was created; we will never train enough specialists—particularly these extreme specialists—to meet the needs of the world. We have to find more innovative ways of getting that expertise to everyone who needs it. We want to make sure that if there's a breakthrough at an MD Anderson or at a Sloan Kettering, that it doesn't take 20 years to get to the front lines of our communities, particularly those who are underserved globally.

CLINICAL ROUNDUP

Early-onset colorectal cancer rising fastest in Western states, say ACS and OSU

Early-onset colorectal cancer is rising most rapidly in Western states, where healthy behaviors are prominent, according to a new study from the American Cancer Society and Ohio State University. The authors of the study, which appears in JNCI, say the findings indicate the need for further etiologic studies to explore early-life colorectal carcinogenesis.

Early-onset colorectal cancer has been on the rise for several decades in the U.S. for unknown reasons. Because geographic differences could help uncover potential causes for the trend, investigators analyzed changes in CRC incidence and risk factors among adults under 50 during 1995-2015 by state and race and ethnicity.

Based on cancer registries representing 95% of the U.S. population, the study found early-onset CRC incidence increased over the most recent ten data years (2006-2015) by 1.1% per year. Rates rose faster for rectal tumors (1.7% per year) than for colon tumors (0.7% per year).

The increase was mostly confined to whites, among whom rates rose in 40 out of 47 states (with available data) and were otherwise stable. The rise varied in magnitude across states, with average increases exceeding 2.5% per year in ten states, six of which are in the west.

For example, over the past two decades CRC incidence increased by 73% in Washington, from 6.7 (per 100,000) during 1995-1996 to 11.5 during 2014-2015, and by 57% in Colorado, from 6.0 to 9.5. Increases were generally steeper for rectal than for colon cancer, with rates doubling in some states (e.g. in Colorado, from 1.9 to 4.2), converging with rates for colon cancer.

"Although early-onset colorectal cancer incidence is currently lowest in Western states and highest in Southern states, consistent with the prevalence of established risk factors, like obesity, physical inactivity, and smoking, this pattern may change because the steepest increases are in Western states," said Rebecca L. Siegel, scientific director of surveillance research at American Cancer Society and lead author of the study.

"This finding suggests that early life exposures in addition to the 'usual suspects' may be contributing to the rise in early onset disease. Future studies should explore novel risk factors for colorectal cancer in young adults."

Johns Hopkins researchers design blood test to detect DNA fragments of multiple cancer types

Researchers at the Johns Hopkins Kimmel Cancer Center have developed a blood test that can detect the presence of seven different types of cancer by spotting unique patterns in the fragmentation of DNA shed from cancer cells and circulating in the bloodstream.

In a proof-of-concept study called DELFI, DNA evaluation of fragments for early interception, accurately detected the presence of cancer DNA in 57% to more than 99% of blood samples from 208 patients with various stages of breast, colorectal, lung, ovarian, pancreatic, gastric, or bile duct cancers in the U.S., Denmark, and the Netherlands.

DELFI also performed well in tests of blood samples from 215 healthy individuals, falsely identifying cancer in just four cases.

The test uses machine learning to identify abnormal patterns of DNA fragments in the blood of patients with cancer. By studying these patterns, the investigators said they could identify the cancers' tissue of origin in up to 75% of cases.

The study was published in Nature.

Blood tests, or liquid biopsies, for cancer detection typically look for mutations or for methylation, a chemical reaction in which a methyl group is added to DNA, said senior study author Victor E. Velculescu, professor of oncology and co-director of the Cancer Biology Program at the Johns Hopkins Kimmel Cancer Center.

Not all cancer patients have changes that are detectable using these methods, Velculescu said, and there is a great need for improved methods for early detection of cancer.

DELFI studies the way DNA is packaged inside the nucleus of a cell by looking in the blood at the size and amount of DNA from different regions across the genome for clues to that packaging.

Alessandro Leal, a lead author of the study, said the nuclei of healthy cells package DNA like a well-organized suitcase in which different regions of the genome are carefully placed in various compartments. By contrast, the nuclei of cancer cells are more like disorga-

nized suitcases, with items from across the genome thrown in haphazardly.

"For various reasons, a cancer genome is disorganized in the way it's packaged, which means that when cancer cells die they release their DNA in a chaotic manner into the bloodstream," Jillian Phallen, a lead author on the study and a Johns Hopkins Kimmel Cancer Center postdoctoral fellow, said in a statement. "By examining this cell-free DNA, DELFI helps identify the presence of cancer by detecting abnormalities in the size and amount of DNA in different regions of the genome based on how it is packaged."

The researchers said the test's potential must be further validated in additional studies. If that happens, it could be used to screen for cancer by taking a tube of blood from an individual, extracting the cfDNA, studying its genetic sequences, and determining the fragmentation profile of the cfDNA. The genome-wide fragmentation pattern from an individual can then be compared to reference populations to determine if the pattern is likely healthy or derived from cancer.

Robert B. Scharpf, a senior author on the study and an associate professor of oncology, said because the genome-wide fragmentation patterns may reveal differences associated with specific tissues, these patterns, when found to be derived from cancer, can also indicate the source of the cancer, such as breast, colon, or lung.

DELFI simultaneously analyzes millions of sequences from hundreds to thousands of regions in the genome, identifying tumor-specific abnormalities from minute cfDNA amounts, said Scharpf.

Using DELFI, investigators found genome-wide cfDNA fragmentation profiles are different between cancer patients and healthy individuals.

Stephen Cristiano, a lead author on the study, said, in cancer patients, fragmentation patterns in cfDNA appear to result from mixtures of DNA released from both blood and tumor cells. It also shows multiple distinct genomic differences with increases and decreases in fragment sizes at different regions.

For the current study, the Hopkins investigators worked with colleagues from institutions in the U.S., Denmark, and the Netherlands to perform low-coverage whole genome sequencing of cfDNA from 208 patients with cancer, including 54 breast cancer patients, 27 colorectal cancer patients, 12 lung cancer patients, 28 ovarian cancer patients, 34 pancreatic cancer patients, 27 gastric cancer patients, and 26 bile duct cancer patients. They also performed whole genome sequencing to analyze cfDNA from 215 healthy individuals.

All cancer patient samples were obtained before any treatment, and the majority of the samples, 183, were from people whose disease could be treated with surgical removal of the tumors.

The researchers report the healthy individuals had similar fragmentation profiles, while patients with cancer had more variable fragmentation profiles that were less likely to match healthy profiles.

DELFI detected cancer in 73% of cancer patients overall, while misclassifying four of 215 healthy individuals (98% specificity). The test also was found to be 61%-75% accurate in identifying the tissue of origin of the cfDNA.

When DELFI and mutation-based cfDNA analyses were combined, investigators could accurately detect 91% of cancer patients.

Because the test is easy to administer and employs simple and inexpensive laboratory methods, Velculescu expects the test could ultimately be more cost-effective than other cancer screening tests, including other current cfDNA tests.

DRUGS & TARGETS

FDA approves first mesothelioma treatment in 15 years

FDA has approved a tumor-treating fields device in combination with pemetrexed plus platinum-based chemotherapy for the first-line treatment of unresectable, locally advanced, or metastatic malignant pleural mesothelioma.

The device, the NovoTTF-100L System (Novocure), is the first treatment for MPM approved by the FDA in 15 years, since pemetrexed was approved in 2004.

TTF therapy uses electric fields to disrupt solid tumor cancer cell division. Previously, FDA approved Optune, another TTF delivery system from Novocure, for the treatment of glioblastoma in 2011.

MPM is a rare but aggressive cancer strongly associated with asbestos exposure. Prior to the new approval, pemetrexed plus cisplatin was the only FDA-approved therapy for patients with unresectable MPM, according to a company statement.

The new device for MPM was approved under the Humanitarian Device Exemption, which was created to encourage innovation in rare diseases.

FDA approval is based on the results of the STELLAR trial, a prospective, single-arm trial of NovoTTF-100L plus chemotherapy first-line in patients with unresectable MPM.

In the trial, 80 unresectable MPM patients treated with TTF plus chemotherapy experienced a median overall survival of 18.2 months. However, Novocure acknowledged "the effectiveness of this device for this use has not been demonstrated."

Median OS was 21.2 months for patients with epithelioid MPM (n = 53) and 12.1 months for patients with non-epithelioid MPM (n = 21). More than half (62%) of patients were alive at 1 year.

The overall response rate was 40%, all were partial responses. In addition, 57% had stable disease; the remaining 3% of patients had progressive disease. At least one follow-up CT scan was performed in most patients (n = 72).

Median progression-free survival was 7.6 months.

Trial results show NovoTTF-100L can be combined with chemotherapy, as there was no increase in serious systemic adverse events when the two modalities were joined. Mild-to-moderate skin irritation was the most common device-related side effect.

FDA approves Piqray + fulvestrant in breast cancer

FDA has approved Piqray (alpelisib, formerly BYL719) in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor positive, human epidermal growth factor receptor-2 negative, PIK-3CA-mutated, advanced or metastatic breast cancer, as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

Piqray is sponsored by Novartis.

Approximately 40% of patients living with HR+/HER2- breast cancer have PIK3CA. PIK3CA mutations are associated with tumor growth, resistance to endocrine treatment, and a poor overall prognosis. Piqray targets the effect of PIK3CA mutations and may help overcome endocrine resistance in HR+ advanced breast cancer.

FDA approval is based on the results of the phase III trial, SOLAR-1, that showed Piqray plus fulvestrant nearly doubled median progression-free survival compared to fulvestrant alone in HR+/HER2- advanced breast cancer patients with a PIK3CA mutation (median PFS 11.0 months vs. 5.7 months; HR=0.65, 95% CI: 0.50-0.85; p<0.001). Piqray provided consistent PFS results across pre-specified subgroups, including among patients previously treated with a CDK4/6 inhibitor.

Overall response rate more than doubled when Piqray was added to fulvestrant in patients with a PIK3CA mutation (ORR= 35.7% vs 16.2% for fulvestrant alone, p=0.0002).

Piqray and its associated companion diagnostic test from QIAGEN N.V. was the first combination product approved under the FDA Oncology Center of Excellence Real-Time Oncology Review pilot program.

"Today's approval is expected to change the way we practice medicine in advanced breast cancer. For the first time, physicians can test for PIK3CA biomarkers and develop a treatment plan based on the genomic profile of a patient's cancer," said Fabrice André, global SOLAR-1 principal investigator, research director and head of INSERM Unit U981, professor in the Department of Medical Oncology at Institut Gustave Roussy in Villejuif, France.

"In the SOLAR-1 phase III trial, alpelisib plus fulvestrant nearly doubled median PFS and more than doubled overall response rate in patients with a PIK3CA mutation, offering them new hope for longer life without progression."

Patients with HR+/HER2- advanced breast cancer can be selected for treatment with Piqray based on the presence of PIK3CA mutations. Concurrent with the approval of Piqray, the therascreen PIK3CA companion diagnostic test from QIAGEN was also approved by the FDA and is now available for patient testing.

SOLAR-1 is a global, phase III randomized, double-blind, placebo-controlled trial studying Piqray in combination with fulvestrant for postmenopausal women, and men, with PIK3CA-mutated HR+/HER2- advanced or metastatic breast cancer that progressed on or following aromatase inhibitor treatment with or without a CDK4/6 inhibitor. SOLAR-1 is the pivotal phase III trial that supported this approval.

The trial randomized 572 patients. Patients were allocated based on central tumor tissue assessment to either a PIK-3CA-mutated cohort (n=341) or a PIK3CA non-mutated cohort (n=231).

Within each cohort, patients were randomized in a 1:1 ratio to receive continuous oral treatment with Piqray (300 mg once daily) plus fulvestrant (500 mg every 28 days + Cycle 1 Day 15) or placebo plus fulvestrant.

Stratification was based on visceral metastases and prior CDK4/6 inhibitor treatment. Patients and investigators are blinded to PIK3CA mutation status and treatment.

The primary endpoint is local investigator assessed PFS using RECIST 1.1 for

patients with a PIK3CA mutation. The key secondary endpoint is overall survival. Secondary endpoints include, but are not limited to, overall response rate, clinical benefit rate, health-related quality of life, efficacy in PIK3CA non-mutated cohort, safety, and tolerability. SOLAR-1 is ongoing to assess overall survival and other secondary endpoints.

FDA approves lenalidomide for follicular and marginal zone lymphoma

FDA approved lenalidomide (Revlimid) in combination with a rituximab product for previously treated follicular lymphoma and previously treated marginal zone lymphoma.

The drug is sponsored by Celgene Corp.

Approval was based on two clinical trials: AUGMENT (NCT01938001) and MAGNIFY (NCT01996865). In AUGMENT, 358 patients with relapsed or refractory FL or MZL were randomized (1:1) to receive lenalidomide and rituximab or rituximab and placebo. In the single-arm component of MAGNIFY, 232 patients with relapsed or refractory FL, MZL, or mantle cell lymphoma received 12 induction cycles of lenalidomide and rituximab.

In AUGMENT, the primary endpoint was progression-free survival in the intent-to-treat population, as determined by an independent review committee. Median PFS was 39.4 months (95% CI: 22.9, NE) in the lenalidomide arm and 14.1 months (95% CI: 11.4, 16.7) in the placebo-containing arm (HR 0.46; 95% CI: 0.34, 0.62; p<0.0001).

The objective response rate by IRC assessment for patients with follicular lymphoma was 80% (118/147; 95% CI: 73%, 86%) in the lenalidomide arm compared with 55.4% (82/148; 95% CI: 47%, 64%) in the control arm.

For patients with marginal zone lymphoma, the ORR by IRC assessment was 65% (20/31; 95% CI: 45%, 81%) compared with 44% (14/32; 95% CI: 26%, 62%), respectively.

In MAGNIFY, the ORR by investigator assessment was 59% (104/177; 95% CI: 51%, 66%) for patients with follicular lymphoma. Median response duration was not reached with a median follow-up of 7.9 months (95% CI: 4.6, 9.2). For patients with marginal zone lymphoma, the ORR by investigator assessment was 51% (23/45; 95% CI: 36%, 66%). Median response duration was not reached with a median follow-up of 11.5 months (95% CI: 8.0, 18.9).

The recommended lenalidomide dose for FL or MZL is 20 mg once daily orally on days 1-21 of repeated 28-day cycles for up to 12 cycles.

FDA approves gilteritinib for refractory AML

FDA approved the addition of overall survival data in labeling for gilteritinib (Xospata), which is indicated for adult patients who have relapsed or refractory acute myeloid leukemia with a FLT3 mutation as detected by an FDA-approved test.

The drug is sponsored by Astellas Pharma US, Inc.

Approval was based on the ADMIRAL trial (NCT02421939), which included 371 adult patients with relapsed or refractory AML having a FLT3 ITD, D835, or I836 mutation identified by the LeukoStrat CDx FLT3 Mutation Assay.

Patients were randomized (2:1) to receive Xospata 120 mg once daily (n=247) over continuous 28-day cycles or prespecified salvage chemotherapy (n=124). Salvage chemotherapy included either intensive cytotoxic chemotherapy or a low-intensity regimen.

For the analysis, OS was measured from the randomization date until death by any cause. The median OS was 9.3 months for patients receiving gilteritinib and 5.6 months for those on the chemotherapy arm (HR 0.64; 95% CI: 0.49,0.83; 1 sided p-value=0.0004).

The results were consistent in the intensive chemotherapy stratum (HR 0.66; 95% CI: 0.47-0.93) and the low-intensity regimen stratum (HR 0.56; 95% CI: 0.38-0.84).

The recommended gilteritinib dose is 120 mg orally once daily.

We are at the ASCO annual meeting in Chicago this weekend.